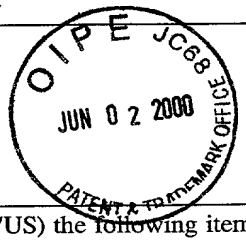
416 Rec'd PCT/PTO 02 JUN 2000

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	Attorney's Docket Number 045636-5033	U.S. Application No. Unassigned 09/555640
International Application. No.	International Filing Date	Priority Date Claimed
PCT/FR98/02615	3 December 1998	3 December 1997



Title of Invention
ERYTHROVIRUS AND ITS APPLICATIONS

Applicants For DO/EO/US
Quang Tri NGUYEN, Antoine GARBARG-CHENON and Veronique AUGUSTE

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventors (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 14. below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [X] Other items or information:
    a. [X] WIPO Publication WO99/28439 (first page)
    b. [X] PCT/IB/304
    c. [X] PCT/IB/308
    d. [X] Sequence Listing (paper copy only)

U.S. APPLICATION NO.	INTERNATIONAL APPLICATION NO.	ATTORNEY DOCKET NUMBER
Unassigned	PCT/FR98/02615	045636-5033

09/555640

5. [X] The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)):			
Search Report has been prepared by the EPO or JPO.....$840.00			
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$670.00			
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$760.00			
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$970.00			
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$96.00			
ENTER APPROPRIATE BASIC FEE AMOUNT =			$ 840.00
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] **20** [ ] **30** months from the earliest claimed priority date (37 CFR 1.492(e)).			$
Claims	Number Filed	Number Extra	Rate	
Total Claims	34 - 20 =	14	X $18.00	$252.00
Independent Claims	5 - 3 =	2	X $78.00	$156.00
Multiple dependent claim(s) (if applicable)			+$260.00	$
TOTAL OF ABOVE CALCULATIONS =				**$1248.00**
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)				-$
SUBTOTAL =				**$1248.00**
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+$
TOTAL NATIONAL FEE =				**$1248.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property				+$
TOTAL FEES ENCLOSED =				**$1248.00**
			Amount to be refunded	$
			charged	$

a. [ ] A check in the amount of____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 50-0310 in the amount of **$1248.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] **Except** for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 CFR §1.16 and §1.17 which may be required, or credit any overpayment to Deposit Account No. 50-0310.

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Submitted: June 2, 2000

Attorney Docket No.045636-5033

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of : Quang Tri NGUYEN, et al.	
U.S. National Phase Application Filed : June 2, 2000	
U.S. Application No.: To Be Assigned	Group Art Unit: Unassigned
Date of National Stage Entry : Concurrently	Examiner: Unassigned
Based on PCT/FR98/02615 Filed : December 3, 1998	
For: ERYTHROVIRUS AND ITS APPLICATIONS	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to the examination of the above-identified application on the merits, please amend the application, without prejudice, as follows:

IN THE CLAIMS:

Claim 1, lines 1 and 2, change "Nucleic acids sequence, characterized in that it is" to--A nucleic acid comprising nucleic acids--

Claim 2, line 1, change, "Nucleic sequence according to" to --The nucleic acids of--;

Claim 2, line 2, change "characterized in that it has" to --wherein the nucleic acids exhibits--

Claim 3, line 1, change "sequence SEQ ID NO:1," to --the nucleic acids--;

Claim 3, line 11, change "the fragments of" to --wherein the fragments comprise--;

Claim 4, lines 1 and 2, change "Fragment according to Claim 3, characterized in that it is" to --A fragment according to Claim 3,--;

Claim 4, line 6, change "in that it" to --wherein the selected sequence--;

Claim 5, lines 1 and 2, change "Fragment according to Claim 3, characterized in that it is" to --A fragment according to Claim 3,--;

Claim 5, line 7 change "in that it is" to --wherein the selected sequence--;

Claim 6, line 1, change "Pairs" to ---A pair--;

Claim 7, line 1, change "Variant" to --A variant--;

Claim 8, line 1, change "Plasmid," to -- A plasmid--;

Claim 9, line 1, change "Plasmid" to --A plasmid--;

Claim 10, line 1, change "Diagnostic" to --A diagnostic--;

Claim 10, line 4, insert "and" before "the";

Claim 10, lines 6 and 7, delete ", optionally labelled with an appropriate marker";

Claim 11, line 1, change "Method" to --A method--;

Claim 12, line 1, change "Method" to --The method--;

Claim 13, line 1, change "Method" to --The method--;

Claim 13, lines 3, delete "according to Claim 6" and add:

--selected from the group consisting of:

pair A: primers SEQ ID NO:111 and SEQ ID NO:112;

pair B: primers SEQ ID NO:105 and SEQ ID NO:106;

pair C: one of the sequences SEQ ID NO:2-44, 105, 106, 107, 109, 111 or 112 and one of the sequences SEQ ID NO:45-80 108 or 110;

pair D: primer SEQ ID NO:107 and primer SEQ ID NO:109;

paid E: two primers selected from the sequences SEQ ID NO:2-44, 105, 106, 107, 109, 111 or 112; and

pair F: two primers selected from the sequences SEQ ID NO:45-80, 108 or 110.--

Claim 14, line 1, change "Method" to --A method--;

Claim 15, please cancel the entire claim;

Claim 16, line 1, change "Method" to --A method--;

Claim 16, lines 5 and 6, please delete "optionally labeled";

Claim 17, line 1, change "Products" to --A product--;

Claim 17, line 2, change "they are" to --it is--;

Claim 18, line 1, change "Protein" to --A protein--;

Claim 19, line 1, change "Protein or peptide, characterized in that it is" to --A protein or peptide,--;

Claim 19, line 3, delete the phrase, "in that it is";

Claim 20, line 1, change "Immunogenic compositions" to --An immunogenic composition--

Claim 20, lines 3 and 4, delete "and/or one of the peptides or proteins according to Claim 18 or Claim 19";

Claim 21, line 1, change "Antibodies" to --An antibody--;

Claim 21, lines 2 and 3, change "any one of Claims 17 to 20" to --Claim 17--;

Claim 22, please delete in its entirety;

Claim 23, please delete in its entirety;

Please add the following new claims, 24-37:

24. A method of *in vitro* screening diagnosis of infection of an individual with an erythrovirus comprising detecting hybridization of the individual's nucleic acid with a nucleic acid according to Claim 1.

25. The method of claim 24 comprising gene amplification.

26. The method of claim 16 wherein the probe is labeled.

27. The method of claim 16 wherein the nucleic acid of the virus to be typed is labeled.

28. An immunogenic composition comprising one or more of the proteins of claim 18.

29. An immunogenic composition comprising one or more of the peptides or proteins of claim 19.

30. An antibody directed against one or more of the proteins of claim 18.

31. An antibody directed against one or more of the proteins of claim 19.

32. A method for the immunological *in vitro* screening diagnosis of infection of an individual with an erythrovirus comprising detecting anti-erythrovirus V9 antibodies by contacting a biological sample with a peptide according to claim 17 and detecting the association of such a peptide with antibodies contained in the biological sample by an appropriate means.

33. The method of claim 32 wherein the appropriate detection means is selected from the group consisting of EIA, ELISA, RIA, and fluorescence.

34. A method for the immunological *in vitro* screening diagnosis of infection of an individual with an erythrovirus comprising detecting erythrovirus V9 viral proteins by contacting a biological sample with an antibody according to claim 21 and detecting the association of such an antibody with erythrovirus V9 viral proteins contained in the biological sample by an appropriate means.

35. The method of claim 34 wherein the appropriate detection means is selected from the group consisting of EIA, ELISA, RIA, and fluorescence.

36. An erythrovirus diagnostic kit comprising at least one probe of sequence SEQ ID NO: 45-80, 108 or 110, and/or a pair of primers selected from the group consisting of , and/or a peptide encoded by, or capable of being expressed with the aid of a nucleic acid of Claim 1, and/or an antibody directed against such peptides.

37. The diagnostic reagent of claim 10 wherein the reagent is labeled with an appropriate marker.

REMARKS

The changes to the claims requested above have been made so as to eliminate multiple claim dependencies and to present claim language more conventional for practice in the United States. These changes do not introduce new matter, nor do they alter the subject matter presented and examined in the corresponding International Application.

Respectfully submitted,

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ERYTHROVIRUS AND ITS APPLICATIONS

The present invention relates to nucleic sequences derived from a human erythrovirus, to their fragments as well as to their applications as diagnostic reagent and as an immunogenic agent.

Sero-epidemiological studies show that infection with the parvovirus B19, recently renamed erythrovirus B19, is commonly and widely distributed worldwide.

In Europe, the seroprevalence for erythrovirus B19 is about 10% in subjects under 5 years, about 50% for subjects over 20 years and greater than 90% in elderly persons.

The high seroprevalence rate suggests that erythrovirus B19 is highly contagious. During epidemics, the rate of transmission to subjects in close contact is 10 to 60%, the route of transmission being mainly aerial (respiratory secretions).

Erythrovirus B19 is a specifically human virus. Acute infection commonly causes benign maculopapular skin rashes in children (epidermal megalerythema or 5th disease). Arthralgias may accompany the rashes and may exceptionally become chronic.

A transient acute erythroblastic attack usually occurs in patients already carrying a chronic haemolytic anaemia (sickle cell anaemia, thalassaemia, pyruvate kinase deficiency and the like), causing a transient aregenerative acute anaemia.

Acute primary infection with erythrovirus B19 is particularly dangerous in pregnant women with a risk of transmission to the foetus estimated at 30%. The risk of foetal death by anaemia, hepatic insufficiency, cardiac insufficiency and foetoplacental anasarca is estimated at between 5 and 9%.

Chronic infections with erythrovirus B19 are found essentially in immunosuppressed subjects (chronic myeloid leukaemia, humoral and cellular immune

deficiency, organ or marrow transplants, AIDS diseases).

In seropositive HIV-1 patients, chronic infection with erythrovirus B19 is responsible for chronic anaemia, but can also act on the other lineages (neutropenia and especially thrombopenia). The absence of a sufficient humoral immune response in these patients allows the installation of a chronic erythroviraemia and explains both the chronic erythroblastopenia and the absence of other symptoms such as rash or arthralgias.

Erythrovirus B19 is a virus having a single-stranded DNA genome of about 5.4 kbases; it is the only erythrovirus classified to date; all the strains which have been sequenced and which have been the subject of a publication in the sequence libraries (GenBank or EMBL) exhibit a low genetic variability (98% nucleic sequence similarity over the whole genome and 96% similarity over the VP1 region) (R.O. SHADE, *J. Virol.*, 1986, 58, 3, 921-936, B19-AU).

Virological diagnosis of erythrovirus B19 infections is based essentially on the detection of the viral genome, insofar as the culture cannot be carried out routinely.

For acute infections with erythrovirus B19 (primary infections), this detection can be made by gene amplification (PCR), but also be hybridization (*dot-blot*) given the viral titre, which is usually very high during primary infections (up to 10^{14}/ml of serum); however, the viral titre is much lower during chronic infections and only a gene amplification detection method can be envisaged.

These detection techniques are dependent on the genetic variability of the virus tested for; the reagents prepared from known erythrovirus B19 sequences do not make it possible to detect the variant erythrovirus infections, either by gene amplification or by B19 serodiagnosis.

Indeed, the existing serodiagnostic tests are specific for erythrovirus B19 (International Application PCT WO 91/12269; International Application PCT WO 96/09391 (IDEIA® Parvovirus B19 IgG and IgM, DAKO; Parvovirus B19 IgG and IgM *Enzyme Immunoassay*, BIOTRIN)).

Consequently, the detection techniques specified above risk producing negative results both at the nucleic level and with respect to the antibody response.

The identification and the taking into account of new variants are important for developing:

- reagents for the detection and diagnosis of human erythrovirus infections (serodiagnosis, PCR, hybridization), which are sufficiently sensitive and specific, that is to say which do not lead to false-negative or false-positive results,

- compositions capable of protecting against all erythrovirus infections (vaccines), and

- compositions capable of treating a variant erythrovirus infection (serotherapy, monoclonal antibodies).

The inventors therefore set themselves the aim of providing erythrovirus-derived sequences capable of allowing the detection of a variant erythrovirus (called erythrovirus type V9), that is to say which is genetically distant from erythrovirus B19.

The subject of the present invention is a nucleic acid sequence, characterized in that it is selected from the group consisting of:

- the sequences derived from an erythrovirus which, molecularly, cannot be recognized as an erythrovirus B19 because it exhibits a genetic divergence or distance $\geq$ 10% ($<$ 90% similarity) over the whole genome with respect to the erythrovirus B19 sequences and which exhibit a genetic divergence of less than or equal to 6% ($>$ 94% similarity) with respect to the sequence SEQ ID NO:1,

- the sequence SEQ ID NO:1, and

- the nucleotide sequences capable of hybridizing under stringent conditions with the said sequence ID NO:1.

This variant erythrovirus is called type V9 variant.

Stringent conditions are understood to mean, for the purposes of the present invention, the following conditions:

. hybridization for 3 to 24 h in a 1XSSC buffer containing 50% formamide, at 42°C, and

. 3 washes of 15 min in a 2XSSC buffer, at 60°C.

The sequence SEQ ID NO:1, which corresponds to about 95% of the genome of an erythrovirus type V9 and which includes all the coding sequences, has a restriction map which is different from that of the B19 erythroviruses, in particular as regards the BamHI site (no site), HINDIII site (only one site) and PvuII site (five sites).

More precisely, the sequence SEQ ID NO:1 has a restriction profile which is different from that of erythrovirus B19, in particular by the following restriction sites: AccI, AflIII, AlwI, AlwNI, **ApaI**, AvaI, AvaII, AvrII, **BamHI**, BanI, BanII, BbeI, BbsI, BceFI, BcgI, BcnI, **BglII**, BsgI, BsiEI, BsmI, BsmAI, Bsp120I, BspHI, BspMI, BsrFI, Bst1107I, BstEII, BstUI, Bsu36I, DpnI, DraIII, DsaI, EaeI, EagI, EarI, Ec1136I, EcoNI, Eco109I, EcoRI, EheI, FokI, HaeI, HaeIII, HgaI, HgiAI, HhaI, HincII, **HindIII**, HinPI, HpaI, KasI, MaeII, MboI, McrI, MscI, **MunI**, NarI, NciI, NcoI, NsiI, NspI, Nsp7524I, NspBII, NspCI, PflMI, PmeI, Ppu10I, PpuMI, PstI, **PvuII**, SacI, Sau3AI, ScaI, SfaNI, SfcI, SmaI, SpeI, SphI, SspI, StuI, StyI, SwaI, Tth111I, XbaI, XmaI and their isoschizomers.

The subject of the present invention is also fragments of sequence ID NO:1 which are capable of allowing the detection of an erythrovirus V9 and characterized in that they comprise a nucleotide sequence selected from the group consisting of:

a) a sequence corresponding to positions 328-2340 of SEQ ID NO:1, encoding the NS1 protein (SEQ ID NO:81),

b) a sequence corresponding to positions 1796-2017 of SEQ ID NO:1, encoding the 7.5 kDa protein (SEQ ID NO:83),

c) a sequence corresponding to positions 2336-4678 of SEQ ID NO:1, encoding the VP1 protein (SEQ ID NO:85),

d) a sequence corresponding to positions 2336-3016 of SEQ ID NO:1, encoding the VP1u (SEQ ID NO:87),

e) a sequence corresponding to positions 2523-2828 of SEQ ID NO:1, encoding the X protein (SEQ ID NO:89),

f) a sequence corresponding to positions 3017-4678 of SEQ ID NO:1, encoding the VP2 (SEQ ID NO:91),

g) a sequence corresponding to positions 4488-4883 of SEQ ID NO:1, encoding the 11 kDa protein (SEQ ID:93),

h) a nucleotide sequence capable of hybridizing with one of the sequences SEQ ID NO:1, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:91 or SEQ ID NO:93,

i) the sequences SEQ ID NO:2-80,

j) the sequences SEQ ID NO:105 (E1905f), 106 (E1987r), 107 (E2076f), 108 (E2151r), 109 (E2406r), 110 (E2149rs), 111 (E2717f), 112 (E2901r), 113 (e1855f), 114 (e2960r), 115 (e1863f), 116 (e2953), 117 (e2435fStul/BglII), 118 (e4813rEcoRI), 119 (e3115fBamHI), 120 (e4813rBamHI) and 121 (e1954fp) and

k) the sequences complementary to the preceding sequences, the fragments derived from the preceding sequences of at least 17 nucleotides or their complementary sequences.

For the purposes of the present invention, nucleic sequence or nucleotide sequence (DNA or RNA sequence) is understood to mean one of the sequences as defined above and their complementary sequences (anti-sense sequences) as well as the sequences comprising one or more of the said sequences or fragments thereof.

The invention also includes nucleotide fragments complementary to the preceding ones as well as fragments modified with respect to the preceding

ones by removal or addition of nucleotides in a proportion of about 15%, with respect to the length of the above fragments and/or modified at the level of the nature of the nucleotides, as long as the modified nucleotide fragments retain a capacity for hybridization with the erythrovirus V9 DNA or RNA sequence which is similar to that exhibited by the corresponding unmodified fragments.

Some of these fragments are specific and are used as a probe or primer; they hybridize specifically to an erythrovirus V9 or a related erythrovirus; a virus related to erythrovirus V9 is understood to mean an erythrovirus exhibiting a genetic divergence of less than or equal to 6%; these fragments are selected from the group consisting of the sequences SEQ ID NO:45-80 and NO:108 and 110, or their complementary sequences, the sequences derived from these sequences of at least 17 nucleotides and the sequences comprising the said sequences and they find application in the specific identification of an erythrovirus V9 or of a related erythrovirus.

Others of these fragments are used as primers, for the amplification of sequences derived from an erythrovirus type V9 or a related virus, such as the sequence SEQ ID NO:1; these primers are chosen from the group consisting of the sequences SEQ ID NO:2-44 and the sequences SEQ ID NO:105-109 and 111-121 or their complementary sequences and the sequences derived from the said sequences, of at least 17 nucleotides.

The said fragments also include, in the case of primers, the antisense sequences.

Such sequences find application for the differential identification of erythroviruses (erythrovirus B19 and erythrovirus V9), combined with probes as defined above and/or with suitable restriction enzymes.

The said primers preferably comprise between 17 and 30 nucleotides; preferred primers are the following: the sequence SEQ ID NO:105 (positions 1797-

1815 of the sequence SEQ ID NO:1), which corresponds to the sequence SEQ ID NO:10, the sequence SEQ ID NO:106 (positions 1899-1879 of the sequence SEQ ID NO:1), which corresponds to a fragment of the antisense sequence of the sequence SEQ ID NO:11, the sequence SEQ ID NO:107 (positions 1968-1987 of the sequence SEQ ID NO:1), which corresponds to a fragment of the sequence SEQ ID NO:13, the sequence SEQ ID NO:108 (positions 2061-2043 of the sequence SEQ ID NO:1), which corresponds to a fragment of the antisense sequence of the sequence SEQ ID NO:58, the sequence SEQ ID NO:109 (positions 2317-2298 of the sequence SEQ ID NO:1), which corresponds to a fragment of the antisense sequence of the sequence SEQ ID NO:16, the sequence SEQ ID NO:111 (positions 2609-2627 of the sequence SEQ ID NO:1), which corresponds to a fragment of the sequence SEQ ID NO:19 and the sequence SEQ ID NO:112 (positions 2812-2793 of the sequence SEQ ID NO:1), which corresponds to a fragment of the antisense sequence of the sequence SEQ ID NO:23.

Preferred pairs of primers are the following:

- pair A: primers SEQ ID NO:111 and SEQ ID NO:112;
- pair B: primers SEQ ID NO:105 and SEQ ID NO:106;
- pair C: one of the sequences SEQ ID NO:2-44, 105, 106, 107, 109, 111 or 112 and one of the sequences SEQ ID NO:45-80, 108 or 110;
- pair D: primer SEQ ID NO:107 and primer SEQ ID NO:109;
- pair E: two primers selected from the sequences SEQ ID NO:2-44, 105, 106, 107, 109, 111 or 112;
- pair F: two primers selected from the sequences SEQ ID NO:45-80, 108 or 110.

These various primers can be used, depending on the fragment amplified, as sense primer or as antisense primer.

The subject of the present invention is also a variant erythrovirus, characterized in that its genome cannot be recognized molecularly as an erythrovirus B19, in that it exhibits a divergence of less than or equal to 6% with the sequence SEQ ID NO:1, as defined above, and in that its genome hybridizes specifically, under stringent conditions, as defined above, with one of the sequences SEQ ID NO:45 to 80, 108 and 110, as defined above.

The subject of the present invention is also a plasmid, characterized in that it comprises the viral genome of a variant erythrovirus strain, called erythrovirus V9 or a fragment thereof, which cannot be recognized molecularly as an erythrovirus B19 and which exhibits with the latter a genetic divergence of $\geq 10\%$ over the whole genome with respect to the erythrovirus B19 sequences and a divergence of less than or equal to 6% with the sequence SEQ ID NO:1.

The viral genome of the said erythrovirus V9 is considered to be genetically distant from erythrovirus B19.

According to an advantageous embodiment of the said plasmid, it includes the sequence SEQ ID NO:1 (PCD.V9.C22).

The subject of the present invention is also a diagnostic reagent for the differential detection of type V9 erythroviruses, characterized in that it is selected from the sequences SEQ ID NO:45-80, 108 and 110, optionally labelled with an appropriate marker.

Among the appropriate markers, there may be mentioned radioactive isotopes, enzymes, fluorochromes, chemical markers (biotin and the like), haptens (digoxygenin and the like) and antibodies or appropriate base analogues.

The subject of the present invention is also a process for the rapid and differential detection of erythroviruses, by hybridization and/or gene amplification, using a biological sample as starting

material, which process is characterized in that it comprises:

(1) a step in which a biological sample to be analysed is brought into contact with at least one probe of sequence SEQ ID NO:45-80, 108 or 110, and

(2) a step in which the product(s) resulting from the erythrovirus nucleotide sequence-probe interaction is (are) detected by any appropriate means.

Preferably, the hybridization comprises a pre-hybridization which is carried out in a buffer which comprises 5-60% of formamide; 1-5X SSC; 2% of blocking reagent (*Blocking buffer*, Boehringer Mannheim, Meylan, France); 0.1% of N-laurylsarcosine; 0.01-5% of SDS, at 40-70°C for 90 minutes, and then the hybridization is carried out in 3 ml of a buffer of the same composition with 10 µl of labelled probe at 40-70°C for 1-30 hours.

In accordance with the said process, it may comprise, prior to step (1):

. a step extracting the nucleic acid to be detected, belonging to the virus genome, which may be present in the biological sample, and

. at least one gene amplification cycle.

The gene amplification step is in particular carried out with the aid of one of the following gene amplification techniques: amplification with Qβ-replicase (I. Haruna et al., Proc. Nat. Acad. Sci. USA, 1965, 54, 579-587), PCR (polymerase chain reaction) (R.K. Saiki et al., 1986, Nature, 324:163-6), LCR (*ligase chain reaction*) (F. Barany, Proc. Nat. Acad. Sci. USA, 1991, 88, 189-193), ERA (*end-run amplification*) (C. Adams et al., 1994, *Novel amplification technologies for DNA/RNA-based diagnostics meeting*, San Francisco, CA, United States), CPR (*cycling probe reaction*) (P. Duck et al., Bio-techniques, 1990, 9, 142-147) or SDA (*strand displacement amplification*) (GT. Walker, 1994, *SDA: novel amplification technologies for DNA/RNA-based diagnostics meeting*, San Francisco, CA, United States).

According to an advantageous embodiment of the said process, the amplification cycles are carried out with the aid of a pair of primers selected from the sequences SEQ ID NO:2-44, 105-109 and 111-112 and fragments of these sequences, preferably from the pairs of primers as defined above.

When pair A is used, the amplification product is advantageously screened by the action of the restriction enzyme ApaI (GGGCCC): the product of amplification of a B19 genome is cleaved with ApaI (generating 2 fragments of 149 and 55 base pairs (bp)) whereas the product of amplification of a V9 genome is not cleaved by ApaI (a fragment of 204 bp); an agarose or acrylamide gel electrophoresis makes it possible to distinguish between these restriction fragments.

When pair B is used, the product of amplification is advantageously screened by the action of one of the following restriction enzymes: BglII (AGATCT), or MunI (CAATTG); different fragments are thus obtained depending on whether an erythrovirus V9 or B19 is involved; a fragment which comprises a BglII restriction site is specific for the variant erythrovirus V9 as defined above, whereas the B19 erythroviruses comprise an MunI site in this region. The product of amplification of a B19 genome is cleaved with MunI (generating 2 fragments of 36 and 67 bp) and is not cleaved by BglII (a fragment of 103 bp) whereas the product of amplification of a V9 genome is cleaved by BglII (2 fragments of 19 and 84 bp) and is not cleaved by MunI (a fragment of 103 bp); an agarose or acrylamide gel electrophoresis makes it possible to distinguish between these different restriction fragments.

When pair C is used (a primer capable of hybridizing with all erythroviruses and a primer capable of specifically hybridizing with erythrovirus V9) or when pair F is used (two primers capable of specifically hybridizing with erythrovirus V9), the V9

genome is amplified whereas there is no specific amplification with the B19 genome.

When pair D is used, the product of amplification is advantageously screened by hybridization with a labelled specific probe for erythrovirus V9, selected from the sequences SEQ ID NO:58-60 and 110, preferably by hybridization with the probe of sequence SEQ ID NO:110; the product of amplification of a V9 genome hybridizes specifically with these probes and in particular the probe of sequence SEQ ID NO:110, whereas the product of amplification of a B19 genome does not hybridize with the abovementioned probes.

When pair E is used, the product of amplification is screened by any method of hybridization with a probe specific for erythrovirus V9, selected from the sequences SEQ ID NO:45-80, 108 and 110; in this case, the product of amplification of a V9 genome hybridizes with the probe, but not the product of amplification of a B19 genome.

The subject of the invention is also the use of the sequences described above, of fragments derived from these sequences or of their complementary sequences, for carrying out a method of hybridization or of gene amplification of erythrovirus nucleic sequences, these methods being applicable to the *in vitro* diagnosis of the potential infection of an individual with an erythrovirus type V9.

The subject of the present invention is also a method of screening and typing an erythrovirus V9 or a related virus, characterized in that it comprises bringing a probe selected from the group consisting of the sequences SEQ ID NO:45-80, 108 and 110, optionally labelled, into contact with the nucleic acid of the virus to be typed and detecting the nucleic acid-probe hybrid obtained.

The subject of the present invention is also products of translation, characterized in that they are encoded by a nucleotide sequence as defined above.

The subject of the present invention is also a protein, characterized in that it is in particular capable of being expressed with the aid of a nucleotide sequence selected from the group consisting of the sequences SEQ ID NO:81, 83, 85, 87, 89, 91 and 93, as defined above and the derived peptides comprising between 7 and 50 amino acids.

Peptide is understood to mean below both the proteins and the peptides, as defined above.

Such peptides are in particular capable of being recognized by antibodies induced by an erythrovirus V9 and/or of inducing the production of anti-erythrovirus V9 antibodies.

The said peptides are in particular selected from the sequences SEQ ID NO:82 (NS1 protein), SEQ ID NO:86 (VP1 protein), SEQ ID NO:88 (single VP1 protein), SEQ ID NO:92 (VP2 protein) and SEQ ID NO:95-104, namely fragments of the VP1 protein [VP1a peptide (SEQ ID NO:95); VP1b peptide (SEQ ID NO:96); VP1c peptide (SEQ ID NO:97); peptide VP1d (SEQ ID NO:98); peptide VP1e (SEQ ID NO:99) and peptide VP1f (SEQ ID NO:100)], or fragments of the VP2 protein [peptide VP2a (SEQ ID NO:101); peptide VP2b (SEQ ID NO:102); peptide VP2c (SEQ ID NO:103); peptide VP2d (SEQ ID NO:104)] as well as the derived peptides comprising 7 to 50 amino acids.

The subject of the invention is also immunogenic compositions comprising one or more products of translation of the nucleotide sequences according to the invention and/or one or the peptides as defined above, obtained in particular by synthetic means.

The subject of the invention is also the antibodies directed against one or more of the peptides described above and their use for carrying out in particular a differential in vitro method of diagnosis of the infection of an individual with an erythrovirus.

The subject of the present invention is also a method for the immunological detection of an erythrovirus V9 infection, characterized in that it comprises:

- for the detection of anti-erythrovirus V9 antibodies, bringing a biological sample into contact with a peptide according to the invention (serodiagnosis),

- for the detection of erythrovirus V9 viral proteins, bringing a biological sample into contact with an antibody according to the invention;

the reading of the result being revealed by an appropriate means, in particular EIA, ELISA, RIA, fluorescence.

By way of illustration, such an in vitro method of diagnosis according to the invention comprises bringing a biological sample, collected from a patient, into contact with antibodies according to the invention or peptides according to the invention, and detecting, with the aid of any appropriate method, in particular with the aid of labelled anti-immunoglobulins, immunological complexes formed between the antigens or the antibodies of the erythroviruses which may be present in the biological sample and the said antibodies or the said peptides, respectively.

The reagents according to the invention are in particular useful for the detection of the V9 erythroviruses and related viruses in pregnant women, in HIV-positive patients with anaemia and/or chronic thrombopenia, recipients of organ or marrow transplants, and patients having a central acute anaemia and for whom the tests for the detection of erythrovirus B19 are negative.

The subject of the invention is, in addition, an erythrovirus diagnostic kit, characterized in that it includes at least one reagent according to the invention (probes, pairs of primers, peptides or antibodies).

In addition to the preceding features, the invention further comprises other features which will emerge from the description which follows, which refers to exemplary embodiments of the method which is the

subject of the present invention as well as to the appended drawings, in which:

- Figures 1, 2 and 3 illustrate phylogenetic trees for erythrovirus V9: Figure 1: phylogenetic tree for the complete erythrovirus sequence; Figure 2: phylogenetic tree for the erythrovirus NS1 genes; Figure 3: phylogenetic tree for the erythrovirus VP1 genes;

- Figures 4, 5 and 6 represent the genetic distances for the complete erythrovirus sequences (Figure 4), for the erythrovirus NS1 genes (Figure 5) and for the erythrovirus VP1 genes (Figure 6);

- Figure 7 illustrates the restriction map of sequence ID NO:1.

It should be understood, however, that these examples are given solely by way of illustration of the subject of the invention and do not constitute in any manner a limitation thereto.

EXAMPLE 1: Production of sequences conforming to the invention

An AatII/AatII restriction fragment of 5028 bp, representing virtually the entire (95%) genome of the V9 variant, was cloned into the sequencing vector pcDNA2.1 (Invitrogen, Netherlands) in the following manner.

The single-stranded viral DNA was extracted from the serum of a patient with an acute erythroblastopenic attack with the aid of a QIAamp Blood Kit column (Qiagen S.A., France). Using a step of hybridization in a 50 mM NaCl buffer at 56°C for 16 hours, the viral DNA is converted to double-stranded DNA. Next, 1.3 µg of double-stranded viral DNA is subjected to the AatII restriction enzyme (1.8 U) at 37°C for 2 hours, the restriction enzyme is then inactivated at 65°C for 15 minutes. The product is dialysed on a Millipore® VSWP013000 cellulose acetate and nitrate membrane against water for 2 hours. The double-stranded viral DNA AatII/AatII restriction

fragment thus prepared is frozen at -20°C while awaiting the ligation step.

The vector pcDNA2.1 is modified in order to receive the AatII fragment by site-directed insertion mutation: the EagI restriction site of the multiple cloning site was removed and replaced with an AatII site. The vector pcDNA2.1a thus produced was amplified in bacterial culture and purified with the aid of a QIAfilter Plasmid Maxi Kit (Qiagen S.A., France). Next, 3 µg of the vector pcDNA2.1a is subjected to restriction with the enzyme AatII at 37°C for 1 hour and then dephosphorylated with shrimp alkaline phosphatase (Boehringer Mannheim, Meylan, France). The enzymes are inactivated at 65°C for 15 minutes.

The ligation is carried out with a vector/viral DNA insert molar ratio of 1/1, that is to say 50 ng of vector and 100 ng of viral DNA insert, prepared as described above, with the aid of 1 U of T4 ligase (Life Technologies, France) at 24°C for 16 hours. After a 1/2 dilution, the ligation product is heated at 65°C in order to inactivate the T4 ligase and then cooled on ice. Electrocompetent bacteria Sure® (Stratagene, Heidelberg, Germany) are electrophorized with 2 or 4 µl of this ligation solution (1500 V, 50 µF, 200 Ω) and then incubated with 1 ml of SOC medium (Life Technologies, France) for 1 hour before being spread on a Luria Broth agar medium (Life Technologies, France) containing 100 µg/ml of amoxycillin, 15 µg/ml of tetracycline, 100 µg/ml of IPTG and 50 µg/ml of X-gal.

Twenty four (recombinant) white colonies were selected, their plasmid is extracted by minipreparation of DNA and a rough restriction map (AatII, AatII + BamHI, BamHI, BamHI + BglII, HindII) made it possible to select 2 recombinant clones with an insert having a size and a restriction map compatible with a V9 viral DNA insert.

These 2 clones (2 and 22) were sequenced with the aid of an automated sequencer ABI 377 (Perkin Elmer, France): they indeed contain an insert of

5028 bp, the 2 sequences are identified except at position 1165 (A and G for the clones 2 and 22 respectively). The direct sequence of the V9 viral DNA made it possible to determine that it is the G at position 1165 which is correct; it is therefore clone 22 which was selected (PCD.V9.C22), whose sequence corresponds to SEQ ID NO:1.

Figures 1 to 6 show the genetic distances which exist between erythrovirus V9 and erythrovirus B19. In these figures, the different erythrovirus sequences are represented by their mnemonic in GenBank (*release* 103.0 of October 1997).

EXAMPLE 2: Diagnosis of an erythrovirus type V9 by DNA hybridization (dot blot or slot blot or microplate) with a specific probe

The viral DNA is extracted, for example, with the aid of a QIAamp Blood Kit column (Qiagen S.A., France) or of any other method of extracting nucleic acids from a biological sample (blood, serum, plasma, amniotic fluid, bone marrow, tissue). The DNA in solution is denatured at 95°C for 2 minutes and then cooled on ice, transferred onto nylon or cellulose nitrate membrane by vacuum filtration and then fixed (heating of the membrane at 80°C for 1 hour). The membrane is then hybridized under stringent conditions with a DNA or RNA probe specific for V9, such as the sequence SEQ ID NO:1 or its complementary sequence or a fragment thereof, in particular the sequences SEQ ID NO:45 to SEQ ID NO:80 and 110 and their complementary sequences, or a fragment of these sequences which are appropriately labelled. This labelling may be a labelling with a radioelement (^{32}P, ^{33}P, ^{35}S, ^{3}H, ^{14}C or another radio isotope), a cold labelling (biotin), fluorescent marker, digoxygenin or any other molecule which may be coupled or incorporated into a DNA or RNA fragment and which can be detected by a specific antibody, or by a ruthenium chelate). In the case of a labelling with a radioactive element, the visualization is performed by autoradiography or any other method

allowing the detection of the radioisotope emission (such as Phosphorimager, Molecular Dynamics, Bondoufle, France). In the case of a labelling with biotin, the visualization is performed with the aid of an enzyme/streptavidine conjugate and a suitable visualization substrate. In the case of a fluorescent labelling, the visualization is made with the aid of a fluoro-Imager (Molecular Dynamics, Bondoufle, France) or any other apparatus capable of detecting the fluorescence emission. In the case of a labelling with digoxygenin (or with another antigen), the visualization is made with the aid of an anti-digoxgenin antibody (or an antibody specific for the antigen used for the labelling), coupled directly to an enzyme (alkaline phosphatase, peroxidase or any other enzyme), or in an indirect manner with an anti-digoxygenin antibody (or an antibody specific for the antigen used for the labelling) and an antibody coupled to an enzyme. A substrate suitable for the enzyme of the conjugate is used for the visualization. In the case of a labelling with ruthenium chelate (such as TBR), the visualization is performed by an electro-chemiluminescence reaction (G.F. Blackburn et al., Clin. Chem., 1991, 37:1534-1539).

A variant of this technique comprises the fixing of viral DNA on a microplate or another solid support and hybridization with a labelled probe as specified above.

Another variant of this technique comprises the fixing of an unlabelled probe on a microplate or another solid support and hybridization with the viral DNA of the sample which would have been labelled beforehand.

EXAMPLE 3: Diagnosis of an erythrovirus type V9 by gene amplification (PCR or *polymerase chain reaction*) and hybridization

Viral DNA is extracted from a biological sample (blood, serum, plasma, amniotic fluid, bone marrow, tissue) with the aid of a QIAamp Blood Kit column

(Qiagen S.A., France) or of any other method of extracting nucleic acids.

The PCR is carried out according to the method described by Saiki et al. (Nature, 1986, 324: 163-66) with 10 µl of DNA solution in a final volume of 100 µl of reaction mixture (50 mM KCl; 10 mM Tris-HCl pH 8.3; 2.5 mM $MgCl_2$; 200 µM dNTP; 25 pmol of sense and antisense oligonucleotides) with 1.5 IU of AmpliTaq Gold™ (Perkin Elmer, France). The amplification primers are oligonucleotides of 20 to 25 mers chosen so as to amplify only the DNA of the V9 variant: either the 2 primers (sense and antisense) are fragments of the sequences specific for V9 (SEQ ID NO:45 to 80, 108 and 110) or their complementary sequences, or one of the primers is chosen from the sequences specific for V9 (SEQ ID NO:45-80, 108 and 110) or their complementary sequences whereas the other primer is chosen from the sequences capable of hybridizing both the B19 erythroviruses and the V9 erythroviruses (SEQ ID NO:2 to 44, 105-107, 109 and 111-112) or their complementary sequences. The temperature cycles are applied to the reaction mixture by a thermocycler (T9600, Perkin Elmer, France) according to the following programme:

1 cycle:
- 6 minutes at 95°C

5 cycles:
- 60 seconds at 95°C
- 30 seconds at 60°C
- 30 seconds at 72°C

45 cycles:
- 30 seconds at 95°C
- 30 seconds at 60°C
- 30 seconds at 72°C

1 cycle:
- 5 minutes at 72°C

The product of amplification is deposited on a 1.3% agarose gel so as to be subjected to an electrophoretic separation and a transfer onto a nylon membrane loaded by capillarity according to a

conventional technique (Sambrook J. et al., 1989, *Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory Press, Cold Spring Harbor*).

The probe is an oligonucleotide of 20-30 mers, a fragment of a sequence specific for V9 (SEQ ID NO:45 to 80, 108 and 110) or their complementary sequences. It is labelled in 3' with DIG-dUTP with the aid of the DIG *Oligonucleotide Tailing* kit (Boehringer Mannheim, Meylan, France).

The transfer membrane is prehybridized in a buffer comprising (50% formamide; 5X SSC; 2% of blocking reagent (Boehringer Mannheim, Meylan, France); 0.1% of N-laurylsarcosine; 0.02% of SDS), at 42°C for 90 minutes. The hybridization is carried out in 3 ml of a buffer of the same composition with 10 µl of labelled probe at 42°C for 16 hours. The membrane is washed twice in 2X SSC buffer containing 0.1% SDS at 60°C for 10 minutes, and then twice in 1X SSC buffer containing 0.1% SDS at 60°C for 10 minutes. The membrane is then visualized with DIG *Luminescent Detection Kit* (Boehringer Mannheim, Meylan, France) and an autoradiography.

EXAMPLE 4: Group diagnosis and differential diagnosis of type B19 and V9 erythroviruses by gene amplification and hybridization

The viral DNA is extracted from a biological sample (blood, serum, plasma, amniotic fluid, bone marrow, tissue) with the aid of a QIAamp Blood Kit column (Qiagen S.A., France) or of any other method of extracting nucleic acids.

The PCR is carried out according to the method described by Saiki et al. (Nature, 1986, cited above) with 10 µl of DNA solution in a final volume of 100 µl of reaction mixture (50 mM KCl; 10 mM Tris-HCl pH 8.3; 2.5 mM $MgCl_2$; 200 µM dNTP; 25 pmol of sense and antisense oligonucleotides) with 1.5 IU of AmpliTaq Gold™ (Perkin Elmer, France). The amplification primers are oligonucleotides of 20 to 25 mers chosen so as to amplify the DNA of B19 and of the variant V9: the 2

(sense and antisense) primers are fragments of the sequences capable of hybridizing both with the B19 erythroviruses and with the V9 erythroviruses (SEQ ID NO:2 to 44, 105-107, 109, 111-112) or of their complementary sequences. The temperature cycles are applied to the reaction mixture by a thermocycler (T9600, Perkin Elmer, France) according to the following programme:

1 cycle:
- 6 minutes at 95°C

5 cycles:
- 60 seconds at 95°C
- 30 seconds at 60°C
- 30 seconds at 72°C

45 cycles:
- 30 seconds at 95°C
- 30 seconds at 60°C
- 30 seconds at 72°C

1 cycle:
- 5 minutes at 72°C

The product of amplification is deposited on a 1.3% agarose gel so as to be subjected to an electrophoretic separation and a transfer onto a nylon membrane loaded by capillarity according to a conventional technique (Sambrook J. et al., 1989, cited above).

The probe is an oligonucleotide of 20-30 mers, a fragment of a sequence specific for V9 (SEQ ID NO:45 to 80, 108 and 110) or their complementary sequences, or alternatively specific for B19, or finally which hybridizes both with B19 and with V9 (SEQ ID NO:2 to 44 or 105-107, 109, 111-112), if it is sought to carry out a group diagnosis. It is labelled in 3' with DIG-dUTP with the aid of the DIG *Oligonucleotide Tailing* kit (Boehringer Mannheim, Meylan, France).

The transfer membrane is prehybridized and hybridized under the same conditions as those set out in Example 3.

EXAMPLE 5: Group diagnosis and differential diagnosis of type B19 and V9 erythroviruses by gene amplification and restriction enzymes

Extraction of the viral DNA from a biological sample (blood, serum, plasma, amniotic fluid, bone marrow, tissue) with the aid of a QIAamp Blood Kit column (Qiagen S.A., France) or of any other method of extracting nucleic acids.

The NS1a PCR is carried out according to the method described by Saiki et al. with 5 µl of DNA solution in a final volume of 50 µl of reaction mixture (50 mM KCl; 10 mM Tris-HCl pH 8.3; 2.5 mM $MgCl_2$; 200 µM dNTP; 12.5 pmol of sense and antisense oligonucleotides) with 1.5 IU of AmpliTaq Gold™ (Perkin Elmer, France) and the pair of primer B (sense primer e1905f, SEQ ID NO:105; and the antisense primer e1987r, SEQ ID NO:106) using the following temperature cycles (on a thermocycler T9700, Perkin Elmer, France):

1 cycle:
- 6 minutes at 94°C

5 cycles:
- 30 seconds at 94°C
- 1 minute at 55°C
- 1 minute at 72°C

45 cycles:
- 30 seconds at 94°C
- 30 seconds at 60°C
- 30 seconds at 72°C

1 cycle:
- 7 minutes at 72°C

An aliquot of the product of amplification (10 µl) was deposited on a 2% agarose gel so as to be subjected to an electrophoretic separation and a transfer onto a nylon membrane loaded by capillarity according to a conventional technique (J. Sambrook et al., 1989, cited above). The membrane was hybridized with an oligonucleotide probe of 36 mer, e1954fp (SEQ ID NO:121): ACCAGTATCAGCAGCAGTGGTGGTGAAAGCTCTGAA, a

fragment of the sequence SEQ ID NO:11. This probe allows a detection of type B19 and V9 erythroviruses.

An aliquot of the product of amplification (10 µl) was subjected to the action of the restriction enzyme MunI for 2 hours and then subjected to an electrophoretic separation on a 2% agarose gel. As described above, the erythrovirus type is B19 if there is cleavage, and V9 if there is no cleavage.

Results of the NS1a PCR:

79 samples found to be indeterminate or weakly positive with the old B19 PCR (Lefrere, et al., Transfusion, 1995, 35:389-391) were screened with the aid of the new NS1a PCR (consensus erythrovirus, sequences according to the invention). Of the 79 samples screened, 31 are positive and were typed with the aid of the restriction enzyme MunI: 18 (58%) were found to be of type B19 and 13 (42%) of type V9.

The samples which were positive by NS1a PCR were able to be amplified on 1100 bp by a nested PCR (S1S2 PCR) with the aid of the pair of primers e1855f (SEQ ID NO:113) and e2960r (SEQ ID NO:114) for the first amplification step of 30 cycles (PCRS1), and of the pair of primers e1863f (SEQ ID NO:115) and e2953r (SEQ ID NO:116) for the second amplification step of 50 cycles (PCRS2). 15 samples were found to be positive by S1S2 PCR and sequenced on 1110 bp (13 of type B19 by NS1A PCR and 2 of the variant type). The analysis of the sequences showed that:

- the B primers (sense primer e1905f, SEQ ID NO:105; and antisense primer e1987r, SEQ ID NO:106), are perfectly conserved for all the 15 sequences (of the B19 and variant type) as well as for all the known B19 sequences, confirming their importance for use for a consensus diagnostic test for B19 and V9,

- the probe e1954fp (SEQ ID NO:121), a fragment of the sequence SEQ ID NO:11 is equally well conserved for the 15 sequences as well as for all the known B19 sequences,

- the B19 sequences form a well homogeneous group with less than 1.2% divergence between them (7 B19 sequences of GenBank and the 13 B19 sequences of this study),

- finally for the 2 sequences typed variant erythrovirus by NS1a PCR with MunI digestion, less than 4.5% divergence with V9 is observed.

EXAMPLE 6: Cloning of the capsid genes VP1 and VP2 of V9 into a baculovirus expression vector

First step:

- cloning of the VP1 gene into a bacterial plasmid

The VP1 gene of V9 is amplified by PCR according to the method described by Saiki et al. (Nature, 1986, 324:163-166) with 10 µl of a 10^{-2} dilution of V9 viral DNA in a final volume of 100 µl of reaction mixture (20 mM Tris-HCl pH 8.8; 10 mM KCl, 10 mM $(NH_4)_2SO_4$; 2 mM $MgSO_4$; 0.1% Triton X-100; 0.1 mg/ml of BSA; 0.2 mM dNTP; 25 pmol of sense primers (e2435fStuI/BglII: AAAGGCCTAGATCTTGTAGATTATGAGTAAAAC, SEQ ID NO:117) and antisense primers (e4813rEcoRI: GGGAATTCGGTGGGTGACGGTTCCTG, SEQ ID NO:118) with 2.5 U of Pfu Turbo™ (Stratagene, France). The amplification primers were chosen on the V9 sequence on either side of the VP1 gene, their 5' end was modified by addition of restriction site(s) (indicated in their name) in order to facilitate the cloning. The temperature cycles applied to the reaction mixture are the following:

1 cycle:

- 1 minute at 94°C

20 cycles:

- 1 minute at 94°C
- 1 minute at 55°C
- 2.5 minutes at 72°C

1 cycle:

- 10 minutes at 72°C

The product of amplification of the VP1 gene was purified with the aid of a silica column (QIAquick PCR Purification Kit, Qiagen, France) and then

subjected to the action of the restriction enzymes StuI and EcoRI. After heat inactivation of the restriction enzymes (20 min at 65°C), the VP1 gene fragment was purified by dialysis against H_2O on a 0.025 µm filter (VSWP01300, Millipore).

The plasmid pBacPAK8 (Clontech, France) is subjected to the action of the restriction enzymes StuI and EcoR1, the vector is then dephosphorylated with shrimp alkaline phosphatase (Boehringer, France). After heat inactivation of the restriction enzymes (20 min at 65°C), the plasmid was purified with the QIAquick PCR Purification Kit (Qiagen).

The ligation is carried out with 50 ng of plasmid pBacPAK8 and 100 ng of VP1 fragment (prepared as described above) with T4 ligase (Life Technologies, France). After heat inactivation of the T4 ligase (10 min at 65°C), 2 µl of ligation product diluted 1/2 with water are electroporated with 25 µl of electro-competent bacteria (Epicurian Coli Sure Electroporation-Competent cells, Strategene). The electroporated bacteria are immediately taken up in 1 ml of SOC medium (2% tryptone, 0.5% of yeast extracts, 10 mM NaCl, 2.5 mM KCl, 10 mM $MgCl_2$, 10 mM $MgSO_4$ and 20 mM glucose), incubated for 1 h at 37°C, with stirring. Next, 10 µl, 100 µl and 890 µl of the transformed bacteria are plated on Lennox agar dishes (10 g/l of peptone, 5 g/l of yeast extracts, 5 g/l NaCl, and 13 g/l agar) containing 50 µg/ml of ampicillin. After 24 h of incubation at 37°C, 24 colonies per construct are subcultured in 5 ml of Lennox medium with 50 µg/ml of ampicillin and incubated for 24 h at 37°C, with stirring.

The plasmid DNA is extracted by alkaline minilysis with the aid of the QIAprep 8 Turbo miniprep kit (Qiagen) and analysed by Stu1/EcoRI and KpnI/-HindIII restriction in order to determine the presence of the insert and its orientation. The clone pB8-VP1.C5 was selected and the recombinant plasmid was checked by sequencing.

- cloning of the VP2 gene into a bacterial plasmid.

The VP2 gene of V9 is amplified by PCR according to the method described by Saiki et al. (Nature, 1986, 324:163-166) with 10 µl of a 10^{-2} dilution of V9 viral DNA in a final volume of 100 µl of reaction mixture (20 mM Tris-HCl pH 8.8; 10 mM KCl, 10 mM $(NH_4)_2SO_4$; 2 mM $MgSO_4$; 0.1% Triton X-100; 0.1 mg/ml of BSA; 0.2 mM dNTP; 25 pmol of sense primers (e3115fBamHI: CACGGATCCATACCCCAGCATGACTTCAG, SEQ ID NO:119) and antisense primers (e4813rBamHI: CACGGATCCGGTGGGTGACGGTTCCTG, SEQ ID NO:120) with 2.5 U of Pfu Turbo™ (Stratagene, France). The amplification primers were chosen on the V9 sequence on either side of the VP2 gene, their 5' end was modified by addition of restriction site(s) (indicated in their name) in order to facilitate the cloning. The temperature cycles applied to the reaction mixture are the following:

1 cycle:
- 1 minute at 94°C

20 cycles:
- 1 minute at 94°C
- 1 minute at 60°C
- 2.5 minutes at 72°C

1 cycle:
- 10 minutes at 72°C

The product of amplification of the VP2 gene was purified with the aid of a silica column (QIAquick PCR Purification Kit, Qiagen, France) and then subjected to the action of the restriction enzymes BamHI. The VP2 gene fragment was purified by the QIAquick PCR Purification Kit (Qiagen).

The plasmid pBacPAK8 (Clontech, France) is subjected to the action of the restriction enzymes BamHI, the vector is then dephosphorylated with shrimp alkaline phosphatase (Boehringer, France). After heat inactivation of the shrimp alkaline phosphatase (20 min at 65°C), the plasmid was purified by phenol/chloroform extraction and precipitated with ethanol.

The ligation is carried out with 50 ng of plasmid pBacPAK8 and 100 ng of VP2 fragment (prepared as described above) with T4 ligase (Life Technologies, France). After heat inactivation of the T4 ligase (10 min at 65°C), 2 µl of ligation product diluted 1/2 with water are electroporated with 25 µl of electrocompetent bacteria (Epicurian Coli Sure Electroporation-Competent cells, Stratagene). The electroporated bacteria are immediately taken up in 1 ml of SOC medium, incubated for 1 h at 37°C, with stirring. Next, 10 µl, 100 µl and 890 µl of the transformed bacteria are plated on Lennox agar dishes containing 50 µg/ml of ampicillin. After 24 h of incubation at 37°C, 24 colonies per construct are subcultured in 5 ml of Lennox medium with 50 µg/ml of ampicillin and incubated for 24 h at 37°C, with stirring.

The plasmid DNA is extracted by alkaline minilysis with the aid of the QIAprep 8 Turbo miniprep kit (Qiagen) and analysed by BamHI and SacI restriction in order to determine the presence of the insert and its orientation. The clone pB8-VP2.C20 was selected and the recombinant plasmid was checked by sequencing: a base A deleted just upstream of the initiator ATG of VP2 can be noted, but this mutation can be ignored: it will not generate the expression of VP2.

Second step:

- Construction of the recombinant baculovirus expressing VP1

The plasmid pB8-VP1.C5 is cotransfected with the baculovirus BacPAk6, linearized with Bsu361 (BacPAK™ Baculovirus Expression System, Clontech), into SF9 insect cells with lipofectin. 2 isolations are performed by the lysis plaque method, the plaques isolated are transferred onto a nitrocellulose membrane, the membrane is then hybridized with a DNA probe specific for the VP1 gene of V9.

The recombinant baculovirus BacPAK6-pB8-VP1.C4.2 was thus selected. The expression of the VP1

protein was verified by Western Blotting on a cellular pellet of SF9 cells infected with this recombinant baculovirus. A band was observed at the expected size of VP1 (about 80 kDa) but which is not recognized by the anti-VP1-B19 monoclonal antibody (Argène, France). It is possible that this monoclonal antibody does not crossreact with the VP1 protein of V9.

The cloning into a baculovirus was verified by sequencing after PCR with the primers Bac1 and Bac2 (Clontech).

- Construction of the recombinant baculovirus expressing VP2

The plasmid pB8-VP2.C20 is cotransfected with the baculovirus BacPAk6, linearized with Bsu361 (BacPAK™ Baculovirus Expression System, Clontech), into SF9 insect cells with lipofectin. 2 isolations are performed by the lysis plaque method, the plaques isolated are transferred onto a nitrocellulose membrane, the membrane is then hybridized with a DNA probe specific for the VP2 gene of V9.

The recombinant baculovirus BacPAK6-pB8-VP2.-C1.3 is selected. The expression of the VP2 protein was verified by Western Blotting on a cellular pellet of SF9 cells infected with this recombinant baculovirus. The anti-VP2-B19 monoclonal antibody (Argène, France) indeed detects a protein with an apparent molecular weight of about 58 kDa which is also clearly visible on the acrylamide gel. Virus-like particles of about 20 to 30 nm in diameter are observed by electron microscopy in the culture supernatants of the SF9 cells after infection with a recombinant baculovirus expressing the VP2 protein of V9. The size and the appearance of the virus-like particles obtained are in every respect in conformity with those described for B19. This observation confirms that the VP2 protein of V9 is produced in a native form by the baculovirus, because it is capable of forming empty capsides by self-assembling.

The cloning into a baculovirus was verified by sequencing after PCR with the primers Bac1 and Bac2 (Clontech).

Third step:

The proteins VP1 and VP2 of V9 expressed in a baculovirus will be purified so as to be used as a target antigen for new serological tests for the diagnosis of erythrovirus V9 infections.

As is evident from the above, the invention is not at all limited to its embodiments, implementations and applications which have just been described more explicitly; it encompasses on the contrary all the variants which may occur to the specialist in this field, without departing from the framework or the scope of the present invention.

CLAIMS

1. Nucleic acid sequence, characterized in that it is selected from the group consisting of:

- the sequence SEQ ID NO:1,

- the genomic sequences of variant erythroviruses, called erythrovirus type V9, which, molecularly, cannot be recognized as an erythrovirus B19 because it exhibits a genetic divergence ≥ 10% over the whole genome with respect to the erythrovirus B19 sequences and which exhibit a genetic divergence of less than or equal to 6% with respect to the sequence SEQ ID NO:1, and

- the erythrovirus genomic sequences capable of hybridizing under stringent conditions with one of the following sequences: SEQ ID NO:45-80, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119 and SEQ ID NO:120.

2. Nucleic sequence according to Claim 1, characterized in that it has a restriction profile according to Figures 7.1 to 7.3.

3. Fragments of sequence SEQ ID NO:1, according to Claim 1, which are capable of allowing the detection of an erythrovirus V9, characterized in that they are selected from the group consisting of:

a) the sequences SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:91 or SEQ ID NO:93,

b) the sequences SEQ ID NO:2-80

c) the sequences SEQ ID NO:105-121, and

d) the sequences complementary to the preceding sequences, the fragments of at least 17 nucleotides derived from the preceding sequences or their complementary sequences.

4. Fragment according to Claim 3, characterized in that it is selected from the group consisting of the sequences SEQ ID NO:45-80, 108 and NO: 110, their complementary sequences, the sequences of at least 17 nucleotides derived from these sequences and the sequences comprising the said sequences and in that it is capable of serving as a probe in the specific identification of an erythrovirus V9 or of a related erythrovirus.

5. Fragment according to Claim 3, characterized in that it is selected from the group consisting of the sequences SEQ ID NO:2-80 and the sequences SEQ ID NO:105-121, their complementary sequences, the sequences of at least 17 nucleotides derived from these sequences and the sequences comprising the said sequences and in that it is capable of serving as a primer for the amplification of sequences derived from an erythrovirus.

6. Pairs of primers, characterized in that they are selected from the group consisting of:

- pair A: primers SEQ ID NO:111 and SEQ ID NO:112;
- pair B: primers SEQ ID NO:105 and SEQ ID NO:106;
- pair C: one of the sequences SEQ ID NO:2-44, 105, 106, 107, 109, 111 or 112 and one of the sequences SEQ ID NO:45-80, 108 or 110;
- pair D: primer SEQ ID NO:107 and primer SEQ ID NO:109;
- pair E: two primers selected from the sequences SEQ ID NO:2-44, 105, 106, 107, 109, 111 or 112; and
- pair F: two primers selected from the sequences SEQ ID NO:45-80, 108 or 110.

7. Variant erythrovirus, characterized in that it cannot be recognized molecularly as an erythrovirus B19 genome, and in that it exhibits a genetic divergence of less than or equal to 6% with the sequence SEQ ID NO:1

and in that its genome hybridizes specifically, under stringent conditions with one of the sequences SEQ ID NO:45 to 80, 108 and 110.

8. Plasmid, characterized in that it comprises the viral genome of a variant erythrovirus strain, called erythrovirus V9, which cannot be recognized molecularly as an erythrovirus B19 and which exhibits with the latter a genetic divergence of $\geq 10\%$ over the whole genome with respect to the erythrovirus B19 sequences and a genetic divergence of less than or equal to 6% with the sequence SEQ ID NO:1 or a fragment thereof, according to Claim 3.

9. Plasmid according to Claim 8, characterized in that it includes the sequence SEQ ID NO:1.

10. Diagnostic reagent for the differential detection of type V9 erythroviruses, characterized in that it is selected from the sequences SEQ ID NO:45-80, 108 and 110, their complementary sequences, the sequences of at least 17 nucleotides, derived from these sequences, optionally labelled with an appropriate marker.

11. Method for the rapid and differential diagnosis of erythroviruses, by hybridization and/or gene amplification, using a biological sample as starting material, which process is characterized in that it comprises:

(1) a step in which a biological sample to be analysed is brought into contact with at least one probe of sequence SEQ ID NO:45-80, 108 or 110, and

(2) a step in which the product(s) resulting from the erythrovirus nucleotide sequence-probe interaction is (are) detected by any appropriate means.

12. Method according to Claim 11, characterized in that it comprises, prior to step (1):

. a step of extracting of the nucleic acid to be detected, belonging to the virus genome, which may be present in the biological sample, and

. at least one gene amplification cycle.

13. Method according to Claim 12, characterized in that the amplification cycles are carried out with the aid of a pair of primers according to Claim 6.

14. Method for the rapid and differential diagnosis of erythroviruses, characterized in that it comprises:

. a step of extracting of the nucleic acid to be detected, belonging to the virus genome, which may be present in the biological sample,

. at least one gene amplification cycle with the aid of a pair of primers according to Claim 6, and

. the detection of the amplified product, on the one hand, by hybridization with the sequence SEQ ID NO:121 and, on the other hand, by the action of the restriction enzyme MunI.

15. Use of the sequences according to any one of Claims 1 to 5, for carrying out a method of hybridization or of gene amplification of erythrovirus nucleic sequences, these methods being applicable to the *in vitro* diagnosis of the potential infection of an individual with an erythrovirus.

16. Method of screening and typing an erythrovirus V9 or a related virus, characterized in that it comprises bringing a probe selected from the group consisting of the sequences according to Claim 4, optionally labelled, into contact with the nucleic acid of the virus to be typed, optionally labelled, and detecting the nucleic acid-probe hybrid obtained.

17. Products of translation, characterized in that they are encoded by a nucleotide sequence according to Claim 1.

18. Protein, characterized in that it is capable of being expressed with the aid of a nucleotide sequence according to Claim 1.

19. Protein or peptide, characterized in that it is derived from a variant erythrovirus type V9, as defined in Claim 1 and in that it is selected from the sequences:

a) SEQ ID NO:82 (NS1 protein), SEQ ID NO:86 (VP1 protein), SEQ ID NO:88 (single VP1 protein), SEQ ID NO:92 (VP2 protein) and SEQ ID NO:95-104, namely fragments of the VP1 protein [VP1a peptide (SEQ ID NO:95); VP1b peptide (SEQ ID NO:96); VP1c peptide (SEQ ID NO:97); peptide VP1d (SEQ ID NO:98); peptide VP1e (SEQ ID NO:99); peptide VP1f (SEQ ID NO:100)], or fragments of the VP2 protein [peptide VP2a (SEQ ID NO:101); peptide VP2b (SEQ ID NO:102); peptide VP2c (SEQ ID NO:103); peptide VP2d (SEQ ID NO:104)], and

b) the sequences derived from sequences a) comprising between 7 and 50 amino acids.

20. Immunogenic compositions comprising one or more products of translation of the nucleotide sequences according to Claim 17 and/or one of the peptides or proteins according to Claim 18 or Claim 19.

21. Antibodies directed against one or more of the peptides or proteins according to any one of Claims 17 to 20.

22. Method for the immunological detection of an erythrovirus V9 infection, characterized in that it comprises:

- for the detection of anti-erythrovirus V9 antibodies, bringing a biological sample into contact with a peptide according to any one of Claims 17 to 19 (serodiagnosis),

- for the detection of erythrovirus V9 viral proteins, bringing a biological sample into contact with an antibody according to Claim 21;

the reading of the result being revealed by an appropriate means, in particular EIA, ELISA, RIA, fluorescence.

23. Erythrovirus diagnostic kit, characterized in that it includes at least one reagent according to Claim 11 and/or a pair of primers according to Claim 6 and/or a peptide according to any one of Claims 17 to 19 and/or an antibody according to Claim 21.

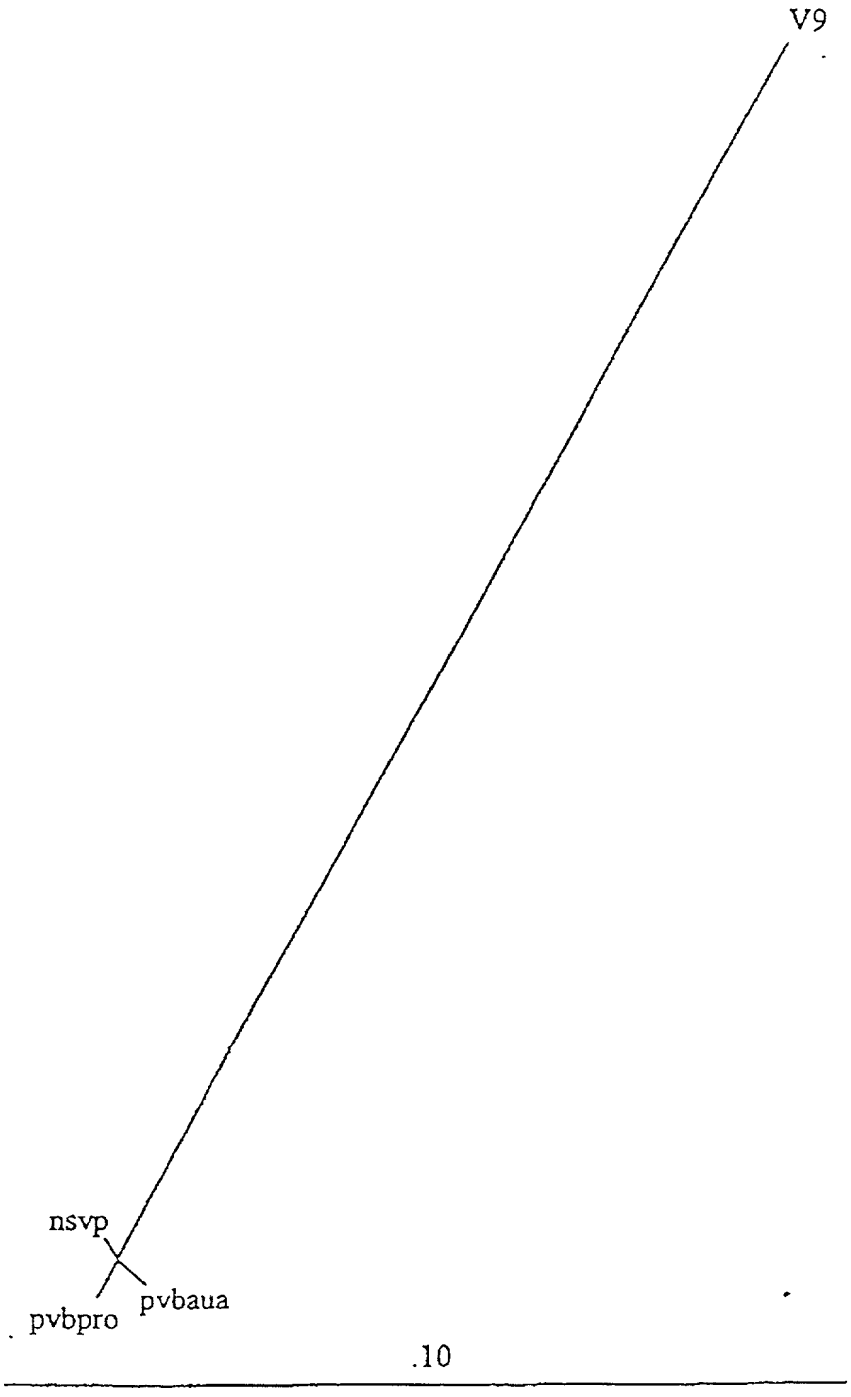
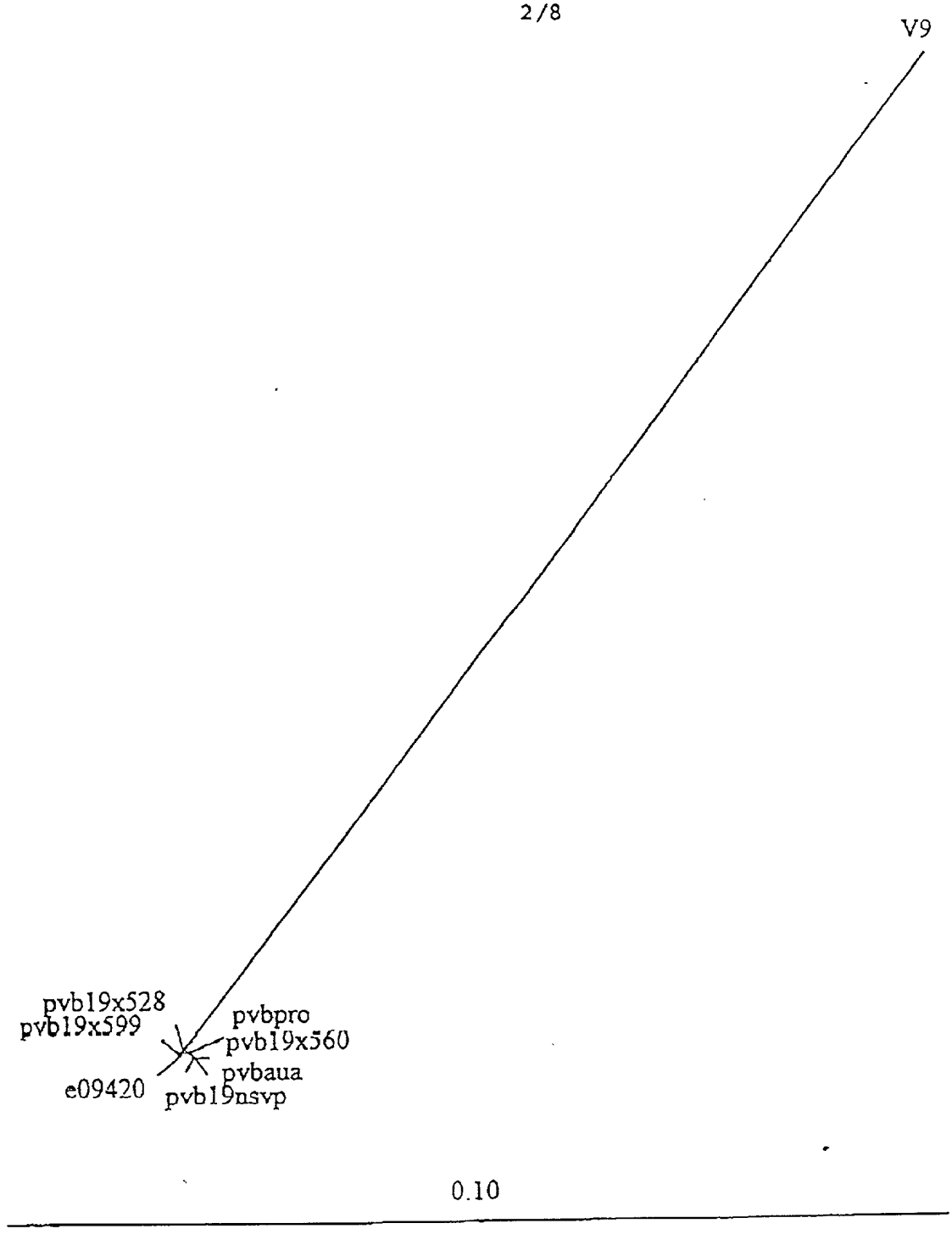


FIGURE 1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pvb19x599
pvbpro
pvb19x560
pvbaua
e09420
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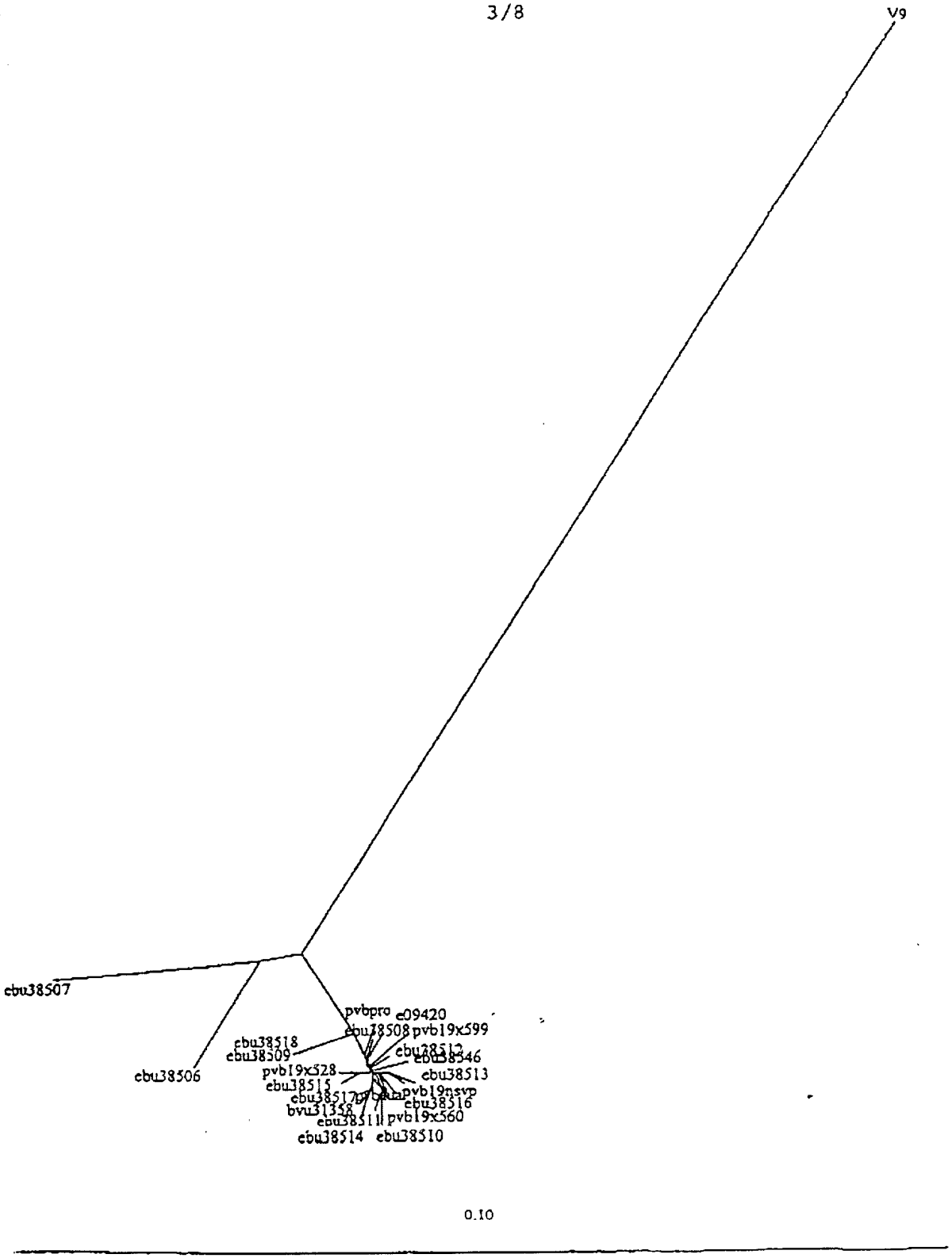
0.10

FIGURE 2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pvb19x528
ebu38513
ebu38515
pvb19nsvp
ebu38516
bvu31358
pvb19x560
ebu38511
ebu38514
ebu38510
0.10

FIGURE 3

09/555640

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PCT/FR98/02615

	nsvp	aua	pro	v9
nsvp	0.00	0.70	0.80	14.77
pvbaua		0.00	0.90	15.03
pvbpro			0.00	15.03
v9				0.00

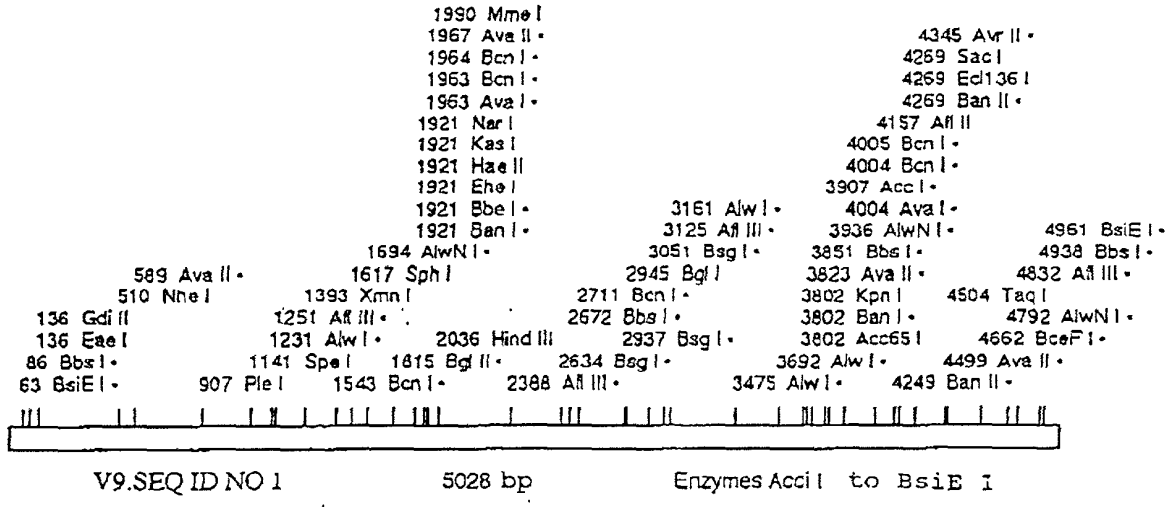
FIGURE 4

	420	599	nsvp	560	aua	528	pro	V9
e09420	0.00	0.65	0.75	0.70	0.80	0.75	0.85	14.87
pvb19x599		0.00	0.70	0.65	0.75	0.70	0.80	14.93
pvb19nsvp			0.00	0.35	0.45	0.70	0.70	14.99
pvb19x560				0.00	0.40	0.65	0.65	14.98
pvbaua					0.00	0.75	0.75	15.06
pvb19x528						0.00	0.80	15.17
pvbpro							0.00	15.11
V9								0.00

FIGURE 5

	510	511	514	515	528	513	nsvp	358	517	508	512	420	516	aua	560	518	546	pro	599	509	506	507	V9
ebu18510	0.00	0.56	0.99	0.95	0.99	0.99	0.90	0.95	0.82	1.08	0.86	1.21	1.03	0.95	0.95	0.95	1.16	1.21	1.29	1.82	3.73	4.59	12.69
ebu18511		0.00	0.77	0.90	0.95	0.95	0.86	0.82	0.69	0.95	0.82	1.08	0.90	0.82	0.82	0.82	0.95	1.08	1.16	1.69	3.64	4.64	12.74
ebu18514			0.00	0.99	0.95	1.03	0.95	0.82	0.77	0.95	0.90	1.16	0.90	0.82	0.82	0.82	1.03	1.16	1.08	1.69	3.73	4.77	13.01
ebu18515				0.00	0.47	0.99	0.90	0.86	0.82	0.90	0.77	1.03	0.86	0.77	0.77	0.77	0.99	0.95	1.08	1.64	3.73	4.59	12.95
pvb19x528					0.00	0.95	0.86	0.90	0.77	0.86	0.82	1.08	0.82	0.73	0.73	0.73	0.95	0.99	1.03	1.60	3.64	4.64	12.85
ebu18513						0.00	0.51	0.99	0.77	0.86	0.82	1.16	0.82	0.73	0.73	0.73	0.95	1.03	1.16	1.69	3.64	4.77	13.05
pvb19nsvp							0.00	0.90	0.69	0.77	0.64	1.08	0.86	0.64	0.64	0.73	0.77	0.82	1.08	1.55	3.41	4.46	12.69
bvu31358								0.00	0.47	0.90	0.86	1.12	0.86	0.77	0.77	0.77	0.99	1.03	1.12	1.69	3.78	4.50	13.01
ebu18517									0.00	0.77	0.73	0.99	0.73	0.64	0.64	0.64	0.86	0.99	0.99	1.55	3.64	4.50	12.90
ebu18508										0.00	0.47	0.73	0.69	0.60	0.64	0.73	0.73	0.90	0.77	1.42	3.55	4.50	13.12
ebu18512											0.00	0.82	0.69	0.60	0.60	0.69	0.64	0.69	0.86	1.38	3.41	4.36	12.95
e09420												0.00	0.69	0.95	0.95	0.95	1.08	1.08	1.12	1.73	3.82	4.78	13.12
ebu18516													1.03	0.95	0.60	0.69	0.73	0.95	0.95	1.51	3.64	4.64	13.17
pvbaua													0.00	0.51	0.51	0.60	0.64	0.86	0.86	1.34	3.55	4.50	12.90
pvb19x560														0.00	0.00	0.60	0.73	0.86	0.95	1.47	3.55	4.55	13.05
ebu18518																0.00	0.82	0.95	0.95	1.47	3.41	4.36	12.95
ebu18546																	0.00	0.90	0.99	1.55	3.55	4.64	13.16
pvbpro																		0.00	1.12	1.16	3.37	4.46	13.00
pvb19x599																			0.00	1.68	3.68	4.68	13.01
ebu18509																				0.00	3.64	4.64	12.64
ebu18506																					0.00	3.51	13.11
ebu18507																						0.00	13.47
V9C																							0.00

FIGURE 6



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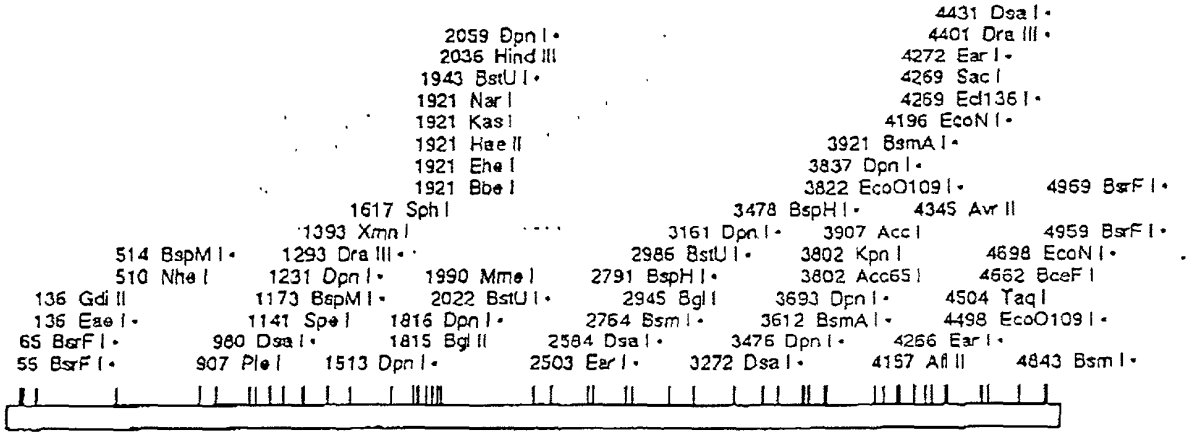
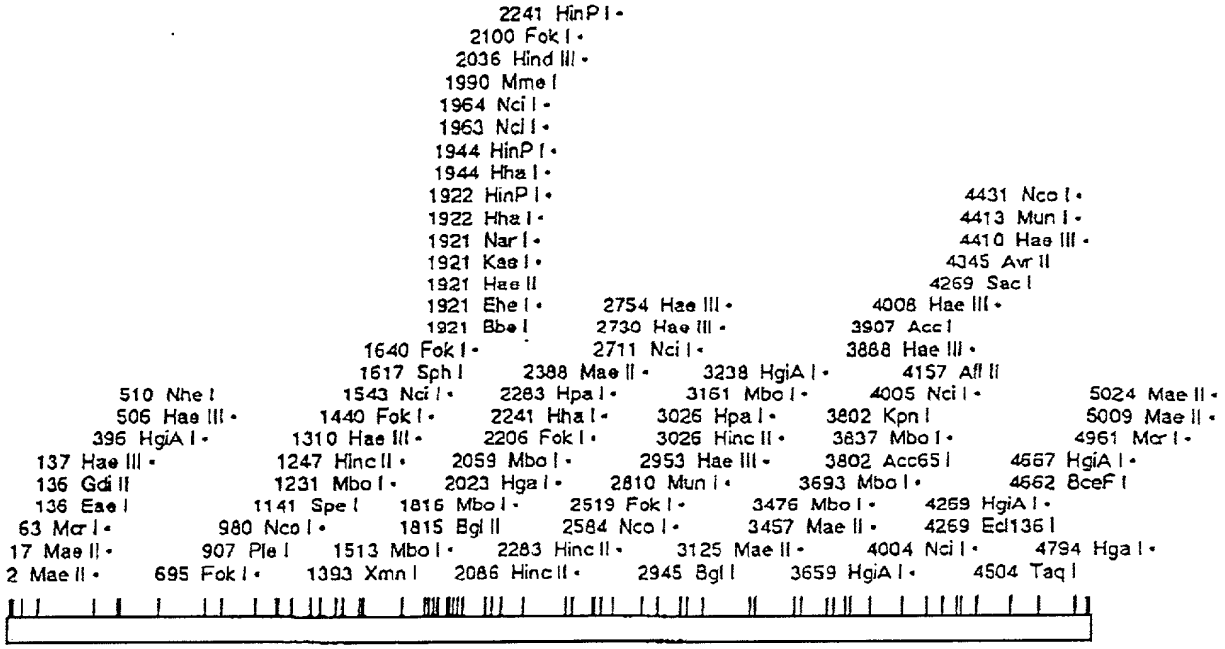


V9.SEQ ID NO 1 5028 bp Enzymes Bsm I to EcoR I

FIGURE 7.1

7/8



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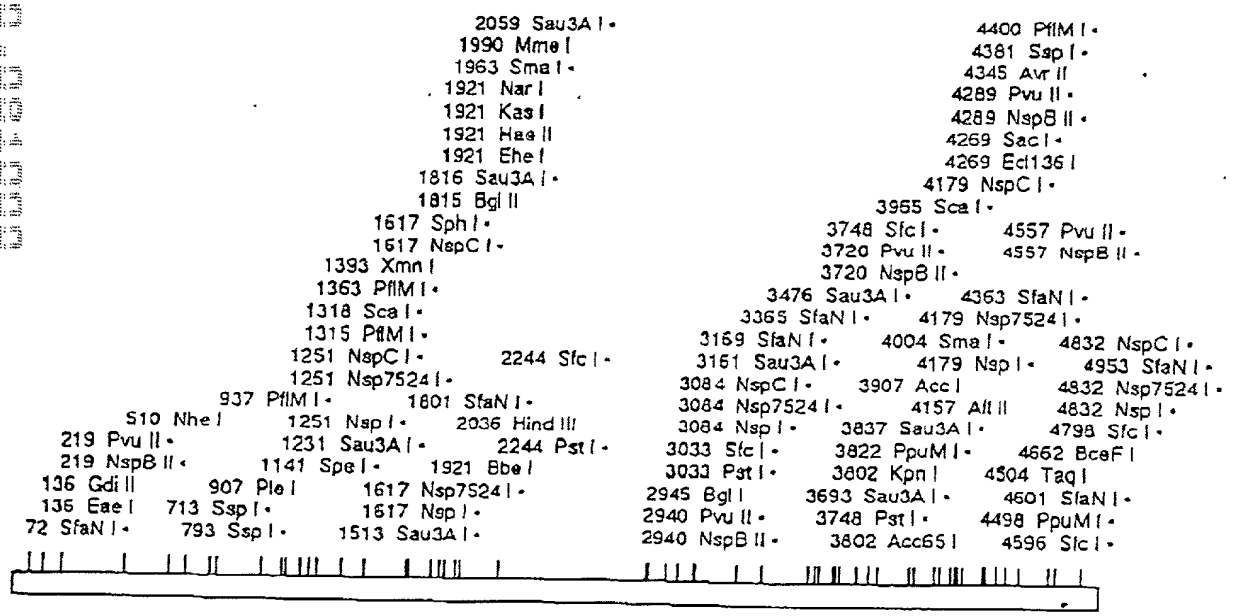
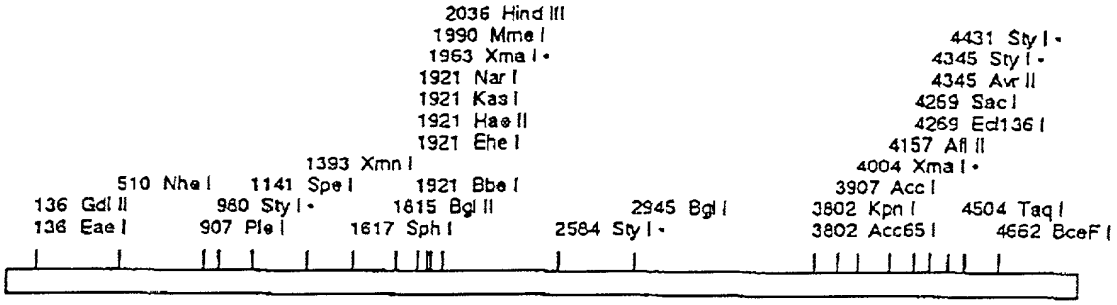


V9.SEQ ID NO 1 5028 bp Enzymes Nci I to Ssp I

FIGURE 7.2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136 Gdl II
980 Sty I
1615 Bgl II
2945 Bgl I
136 Eae I
907 Ple I
1617 Sph I
2584 Sty I
4431 Sty I
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4345 Avr II
4269 Sac I
4269 Ecl136 I
4157 Afl II
4004 Xma I
3907 Acc I
3802 Kpn I
4504 Taq I
3802 Acc65 I
4662 BceF I
V9.SEQ ID NO 1
5028 bp
Enzymes Stu I to Xma I

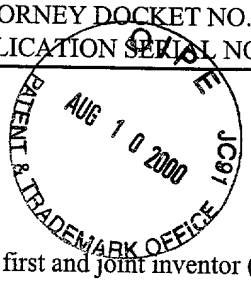
FIGURE 7.3

F 98 02615 FR

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

ATTORNEY DOCKET NO.: 045636-5033
APPLICATION SERIAL NO:



As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ERYTHROVIRUS AND ITS APPLICATIONS

the specification of which:

is attached hereto; or

was filed as United States application Serial No. _____ on June 2, 2000 and was amended on _____(if applicable); or

was filed as PCT international application Number PCT/FR98/02615 on December 3, 1998 and was amended under PCT Article 19 on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office information which is material to the patentability of claims presented in this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate or §365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN APPLICATION(S):

COUNTRY (if PCT, indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
FRANCE	FR 97 15197	3 December 1997	[X] Yes [ ] No
			[ ] Yes [ ] No
			[ ] Yes [ ] No
			[ ] Yes [ ] No

Combined Declaration For Patent Application and Power of Attorney - **(Continued)**
(includes Reference to PCT International Applications)

ATTORNEY DOCKET NO.: 045636-5033

I hereby claim the benefits under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

U.S. PROVISIONAL APPLICATIONS

U.S. PROVISIONAL APPLICATION NO.	U.S. FILING DATE

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to the patentability of claims presented in this application in accordance with Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. APPLICATION NO.	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the registered practitioners of Morgan, Lewis & Bockius LLP included in the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number.

Customer Number: 009629

Direct Telephone Calls To:
(name and telephone number)

Reid G. Adler
202-467-7756

Combined Declaration For Patent Application and Power of Attorney - **(Continued)**
(includes Reference to PCT International Applications)

ATTORNEY DOCKET NO.: 045636-5033

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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FIRST OR SOLE INVENTOR'S SIGNATURE		DATE 17 JUIL. 2000

FULL NAME OF SECOND INVENTOR	**Antoine GARBARG-CHENON**	
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SECOND INVENTOR'S SIGNATURE		DATE 17 JUIL. 2000

FULL NAME OF THIRD INVENTOR	**Véronique AUGUSTE**	
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POST OFFICE ADDRESS	22/30 , rue du Borrego, F-75020 Paris, France	
THIRD INVENTOR'S SIGNATURE		DATE

Listing of Inventors Continued on attached page(s) [ ] Yes [X] No

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AUGUSTE, Véronique
ASSISTANCE PUBLIQUE-HOPITAUX DE PARIS

<120> ERYTHROVIRUS HUMAIN, FRAGMENTS DUDIT VIRUS AINSI QUE LEURS APPLICATIONS

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<400> 6
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<400> 46
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<210> 47
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tggtggtgct ctatgctaga cttagatact tctgactggg 100

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<400> 48
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atgctaaaag accccgcatt actgcaaata cagacagtgc tactaatgaa actggggagt 180

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cccggtgtgc ctgtggttat aacc 84

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ttacttacag aggctg 76

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<400> 57
cacaaagctg gagccactat gaaaactg 28

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<400> 61
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gaaagaggca aaagtgtgca ctattagtcc cattatgggg tactctactc cgtggagata 240

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<400> 73
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<210> 74
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<210> 79
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<210> 80
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<400> 80
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cagacgctgt agaatataaa ttattaacta gatatgaaca acatgtaatt agaatgctaa 180

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<210> 81
<211> 2013
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<213> erythrovirus

<400> 81

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  1               5                  10                  15

tgt gct aat gat aac tgg tgg tgc tct atg cta gac tta gat act tct      96
Cys Ala Asn Asp Asn Trp Trp Cys Ser Met Leu Asp Leu Asp Thr Ser
             20                  25                  30

gac tgg gaa cca cta acc cat tct aac aga tta atg gca ata tat tta     144
Asp Trp Glu Pro Leu Thr His Ser Asn Arg Leu Met Ala Ile Tyr Leu
         35                  40                  45

agc agt gtt gct tct aaa ctt gat ttt act ggg ggg ccg cta gca ggt     192
Ser Ser Val Ala Ser Lys Leu Asp Phe Thr Gly Gly Pro Leu Ala Gly
     50                  55                  60

tgc tta tac ttt ttt cag gtg gaa tgt aac aaa ttt gag gaa ggc tat     240
Cys Leu Tyr Phe Phe Gln Val Glu Cys Asn Lys Phe Glu Glu Gly Tyr
 65                  70                  75                  80

cat atc cat gta gtt att ggt ggt cca gga cta aat gct aga aac tta     288
His Ile His Val Val Ile Gly Gly Pro Gly Leu Asn Ala Arg Asn Leu
                 85                  90                  95

act gtg tgc gta gaa ggt tta ttt aat aat gtt ctt tac cat ctt gta     336
Thr Val Cys Val Glu Gly Leu Phe Asn Asn Val Leu Tyr His Leu Val
            100                 105                 110

act gaa agt gtt aaa ctt aaa ttt ttg cca ggg atg act acc aaa gga     384
Thr Glu Ser Val Lys Leu Lys Phe Leu Pro Gly Met Thr Thr Lys Gly
        115                 120                 125

aaa tat ttt aga gat gga gag cag ttt ata gaa aat tac tta atg aaa     432
Lys Tyr Phe Arg Asp Gly Glu Gln Phe Ile Glu Asn Tyr Leu Met Lys
    130                 135                 140

aaa att cct tta aat gtt gtg tgg tgt gta aca aat att gac ggg tat     480
Lys Ile Pro Leu Asn Val Val Trp Cys Val Thr Asn Ile Asp Gly Tyr
145                 150                 155                 160

ata gac acc tgt att tcc gcc tct ttt cgg cga gga gct tgt cat gct     528
Ile Asp Thr Cys Ile Ser Ala Ser Phe Arg Arg Gly Ala Cys His Ala
                165                 170                 175

aaa aga ccc cgc att act gca aat aca gac agt gct act aat gaa act     576
Lys Arg Pro Arg Ile Thr Ala Asn Thr Asp Ser Ala Thr Asn Glu Thr
            180                 185                 190

ggg gag tct agc tgt gga ggg gga gat gtt gtg cca ttc gct gga aag     624
Gly Glu Ser Ser Cys Gly Gly Gly Asp Val Val Pro Phe Ala Gly Lys
        195                 200                 205

gga aca aaa gcg ggg tta aag ttt caa acc atg gta aat tgg cta tgt     672
Gly Thr Lys Ala Gly Leu Lys Phe Gln Thr Met Val Asn Trp Leu Cys
    210                 215                 220
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gaa aac aga gta ttt act gaa gat aaa tgg aaa tta gtg gat ttt aac     720
Glu Asn Arg Val Phe Thr Glu Asp Lys Trp Lys Leu Val Asp Phe Asn
225                 230                 235                 240

caa tat act tta tta agt agc agt cac agt ggc agc ttt caa att caa     768
Gln Tyr Thr Leu Leu Ser Ser Ser His Ser Gly Ser Phe Gln Ile Gln
                245                 250                 255

agt gcc tta aag tta gct att tat aaa gct act aac tta gta ccc act     816
Ser Ala Leu Lys Leu Ala Ile Tyr Lys Ala Thr Asn Leu Val Pro Thr
            260                 265                 270

agt aca ttc ttg tta cat tca gac ttt gag cag gtt act tgc att aaa     864
Ser Thr Phe Leu Leu His Ser Asp Phe Glu Gln Val Thr Cys Ile Lys
        275                 280                 285

gaa aat aaa ata gta aaa tta tta ttg tgt caa aac tat gat cct ctt     912
Glu Asn Lys Ile Val Lys Leu Leu Leu Cys Gln Asn Tyr Asp Pro Leu
    290                 295                 300

tta gtg ggt caa cat gtg tta agg tgg att gac aaa aaa tgt ggt aaa     960
Leu Val Gly Gln His Val Leu Arg Trp Ile Asp Lys Lys Cys Gly Lys
305                 310                 315                 320

aaa aac acc ctg tgg ttt tac ggg cca cca agt act gga aaa aca aat    1008
Lys Asn Thr Leu Trp Phe Tyr Gly Pro Pro Ser Thr Gly Lys Thr Asn
                325                 330                 335

ttg gca atg gct att gct aaa act gta cca gtg tat gga atg gtg aat    1056
Leu Ala Met Ala Ile Ala Lys Thr Val Pro Val Tyr Gly Met Val Asn
            340                 345                 350

tgg aat aat gaa aac ttt cca ttt aat gat gta gcg ggg aaa agt ttg    1104
Trp Asn Asn Glu Asn Phe Pro Phe Asn Asp Val Ala Gly Lys Ser Leu
        355                 360                 365

gtg gtc tgg gat gaa ggc att att aag tcc act att gtg gaa gct gca    1152
Val Val Trp Asp Glu Gly Ile Ile Lys Ser Thr Ile Val Glu Ala Ala
    370                 375                 380

aaa gcc att tta ggt ggt cag cca acc agg gta gat cag aaa atg cgt    1200
Lys Ala Ile Leu Gly Gly Gln Pro Thr Arg Val Asp Gln Lys Met Arg
385                 390                 395                 400

ggc agt gtg gca gtg ccc ggt gtg cct gtg gtt ata acc agc aat ggt    1248
Gly Ser Val Ala Val Pro Gly Val Pro Val Val Ile Thr Ser Asn Gly
                405                 410                 415

gac att aca ttt gtt gtg agt ggt aat acc act aca act gtg cat gct    1296
Asp Ile Thr Phe Val Val Ser Gly Asn Thr Thr Thr Thr Val His Ala
            420                 425                 430

aaa gcc tta aag gaa cgg atg gta aag cta aac ttt acc ata aga tgt    1344
Lys Ala Leu Lys Glu Arg Met Val Lys Leu Asn Phe Thr Ile Arg Cys
        435                 440                 445

agc cct gac atg ggt tta ctt aca gag gct gat gta caa caa tgg cta    1392
Ser Pro Asp Met Gly Leu Leu Thr Glu Ala Asp Val Gln Gln Trp Leu
    450                 455                 460
```

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act tgg tgt aat gca caa agc tgg agc cac tat gaa aac tgg gca ata    1440
Thr Trp Cys Asn Ala Gln Ser Trp Ser His Tyr Glu Asn Trp Ala Ile
465                 470                 475                 480

aac tac aca ttt gat ttc cct gga ata aat gca gat gcc ctc cac cca    1488
Asn Tyr Thr Phe Asp Phe Pro Gly Ile Asn Ala Asp Ala Leu His Pro
                485                 490                 495

gat ctc caa acc acc ccc att gtc cca gac acc agt atc agc agc agt    1536
Asp Leu Gln Thr Thr Pro Ile Val Pro Asp Thr Ser Ile Ser Ser Ser
            500                 505                 510

ggt ggt gaa agc tct gaa gaa ctc agt gaa agc agc ttt ttc aac ctc    1584
Gly Gly Glu Ser Ser Glu Glu Leu Ser Glu Ser Ser Phe Phe Asn Leu
        515                 520                 525

atc act cca ggc gcc tgg aac agt gaa acc ccg cgc tct agt acg ccc    1632
Ile Thr Pro Gly Ala Trp Asn Ser Glu Thr Pro Arg Ser Ser Thr Pro
    530                 535                 540

gtc ccc ggg acc agt tca gga gaa tca ttt gtc gga agc cca gtt tcc    1680
Val Pro Gly Thr Ser Ser Gly Glu Ser Phe Val Gly Ser Pro Val Ser
545                 550                 555                 560

tcc gaa gtg gta gcc gcg tcg tgg gag gaa gct ttt tac acg ccg ctt    1728
Ser Glu Val Val Ala Ala Ser Trp Glu Glu Ala Phe Tyr Thr Pro Leu
                565                 570                 575

gcc gat cag ttt cgt gaa ctg tta gta ggg gtt gac ttt gta tgg gat    1776
Ala Asp Gln Phe Arg Glu Leu Leu Val Gly Val Asp Phe Val Trp Asp
            580                 585                 590

ggt gtg agg gga ttg cct gtt tgc tgt gtg gaa cat ata aac aac agt    1824
Gly Val Arg Gly Leu Pro Val Cys Cys Val Glu His Ile Asn Asn Ser
        595                 600                 605

ggg gga ggg ttg ggg ctt tgc cct cat tgt att aat gtg gga gct tgg    1872
Gly Gly Gly Leu Gly Leu Cys Pro His Cys Ile Asn Val Gly Ala Trp
    610                 615                 620

tat aat gga tgg aaa ttt aga gag ttt act cca gac tta gtg cgc tgc    1920
Tyr Asn Gly Trp Lys Phe Arg Glu Phe Thr Pro Asp Leu Val Arg Cys
625                 630                 635                 640

agt tgt cat gta gga gcc tct aac cca ttt tct gtg tta act tgt aaa    1968
Ser Cys His Val Gly Ala Ser Asn Pro Phe Ser Val Leu Thr Cys Lys
                645                 650                 655

aaa tgt gct tac ctg tct gga tta caa agt ttt gta gat tat gag .      2013
Lys Cys Ala Tyr Leu Ser Gly Leu Gln Ser Phe Val Asp Tyr Glu
            660                 665                 670
```

<210> 82
<211> 671
<212> PRT
<213> erythrovirus

<400> 82

```
Met Glu Leu Phe Arg Gly Val Leu His Ile Ser Ser Asn Ile Leu Asp
 1               5                  10                  15

Cys Ala Asn Asp Asn Trp Trp Cys Ser Met Leu Asp Leu Asp Thr Ser
            20                  25                  30

Asp Trp Glu Pro Leu Thr His Ser Asn Arg Leu Met Ala Ile Tyr Leu
        35                  40                  45

Ser Ser Val Ala Ser Lys Leu Asp Phe Thr Gly Gly Pro Leu Ala Gly
    50                  55                  60

Cys Leu Tyr Phe Phe Gln Val Glu Cys Asn Lys Phe Glu Glu Gly Tyr
65                  70                  75                  80

His Ile His Val Val Ile Gly Gly Pro Gly Leu Asn Ala Arg Asn Leu
                85                  90                  95

Thr Val Cys Val Glu Gly Leu Phe Asn Asn Val Leu Tyr His Leu Val
            100                 105                 110

Thr Glu Ser Val Lys Leu Lys Phe Leu Pro Gly Met Thr Thr Lys Gly
        115                 120                 125

Lys Tyr Phe Arg Asp Gly Glu Gln Phe Ile Glu Asn Tyr Leu Met Lys
    130                 135                 140

Lys Ile Pro Leu Asn Val Val Trp Cys Val Thr Asn Ile Asp Gly Tyr
145                 150                 155                 160

Ile Asp Thr Cys Ile Ser Ala Ser Phe Arg Arg Gly Ala Cys His Ala
                165                 170                 175

Lys Arg Pro Arg Ile Thr Ala Asn Thr Asp Ser Ala Thr Asn Glu Thr
            180                 185                 190

Gly Glu Ser Ser Cys Gly Gly Gly Asp Val Val Pro Phe Ala Gly Lys
        195                 200                 205

Gly Thr Lys Ala Gly Leu Lys Phe Gln Thr Met Val Asn Trp Leu Cys
    210                 215                 220

Glu Asn Arg Val Phe Thr Glu Asp Lys Trp Lys Leu Val Asp Phe Asn
225                 230                 235                 240

Gln Tyr Thr Leu Leu Ser Ser Ser His Ser Gly Ser Phe Gln Ile Gln
                245                 250                 255

Ser Ala Leu Lys Leu Ala Ile Tyr Lys Ala Thr Asn Leu Val Pro Thr
            260                 265                 270

Ser Thr Phe Leu Leu His Ser Asp Phe Glu Gln Val Thr Cys Ile Lys
        275                 280                 285

Glu Asn Lys Ile Val Lys Leu Leu Leu Cys Gln Asn Tyr Asp Pro Leu
    290                 295                 300

Leu Val Gly Gln His Val Leu Arg Trp Ile Asp Lys Lys Cys Gly Lys
305                 310                 315                 320
```

```
Lys Asn Thr Leu Trp Phe Tyr Gly Pro Pro Ser Thr Gly Lys Thr Asn
                325                 330                 335

Leu Ala Met Ala Ile Ala Lys Thr Val Pro Val Tyr Gly Met Val Asn
            340                 345                 350

Trp Asn Asn Glu Asn Phe Pro Phe Asn Asp Val Ala Gly Lys Ser Leu
        355                 360                 365

Val Val Trp Asp Glu Gly Ile Ile Lys Ser Thr Ile Val Glu Ala Ala
    370                 375                 380

Lys Ala Ile Leu Gly Gly Gln Pro Thr Arg Val Asp Gln Lys Met Arg
385                 390                 395                 400

Gly Ser Val Ala Val Pro Gly Val Pro Val Val Ile Thr Ser Asn Gly
                405                 410                 415

Asp Ile Thr Phe Val Val Ser Gly Asn Thr Thr Thr Thr Val His Ala
            420                 425                 430

Lys Ala Leu Lys Glu Arg Met Val Lys Leu Asn Phe Thr Ile Arg Cys
        435                 440                 445

Ser Pro Asp Met Gly Leu Leu Thr Glu Ala Asp Val Gln Gln Trp Leu
    450                 455                 460

Thr Trp Cys Asn Ala Gln Ser Trp Ser His Tyr Glu Asn Trp Ala Ile
465                 470                 475                 480

Asn Tyr Thr Phe Asp Phe Pro Gly Ile Asn Ala Asp Ala Leu His Pro
                485                 490                 495

Asp Leu Gln Thr Thr Pro Ile Val Pro Asp Thr Ser Ile Ser Ser Ser
            500                 505                 510

Gly Gly Glu Ser Ser Glu Glu Leu Ser Glu Ser Ser Phe Phe Asn Leu
        515                 520                 525

Ile Thr Pro Gly Ala Trp Asn Ser Glu Thr Pro Arg Ser Ser Thr Pro
    530                 535                 540

Val Pro Gly Thr Ser Ser Gly Glu Ser Phe Val Gly Ser Pro Val Ser
545                 550                 555                 560

Ser Glu Val Val Ala Ala Ser Trp Glu Glu Ala Phe Tyr Thr Pro Leu
                565                 570                 575

Ala Asp Gln Phe Arg Glu Leu Leu Val Gly Val Asp Phe Val Trp Asp
            580                 585                 590

Gly Val Arg Gly Leu Pro Val Cys Cys Val Glu His Ile Asn Asn Ser
        595                 600                 605

Gly Gly Gly Leu Gly Leu Cys Pro His Cys Ile Asn Val Gly Ala Trp
    610                 615                 620
```

```
Tyr Asn Gly Trp Lys Phe Arg Glu Phe Thr Pro Asp Leu Val Arg Cys
625                 630                 635                 640

Ser Cys His Val Gly Ala Ser Asn Pro Phe Ser Val Leu Thr Cys Lys
                645                 650                 655

Lys Cys Ala Tyr Leu Ser Gly Leu Gln Ser Phe Val Asp Tyr Glu
            660                 665                 670
```

<210> 83
<211> 222
<212> DNA
<213> erythrovirus

<400> 83

```
atg cag atg ccc tcc acc cag atc tcc aaa cca ccc cca ttg tcc cag      48
Met Gln Met Pro Ser Thr Gln Ile Ser Lys Pro Pro Pro Leu Ser Gln
            675                 680                 685

aca cca gta tca gca gca gtg gtg gtg aaa gct ctg aag aac tca gtg      96
Thr Pro Val Ser Ala Ala Val Val Val Lys Ala Leu Lys Asn Ser Val
        690                 695                 700

aaa gca gct ttt tca acc tca tca ctc cag gcg cct gga aca gtg aaa     144
Lys Ala Ala Phe Ser Thr Ser Ser Leu Gln Ala Pro Gly Thr Val Lys
    705                 710                 715

ccc cgc gct cta gta cgc ccg tcc ccg gga cca gtt cag gag aat cat     192
Pro Arg Ala Leu Val Arg Pro Ser Pro Gly Pro Val Gln Glu Asn His
720                 725                 730                 735

ttg tcg gaa gcc cag ttt cct ccg aag tgg                             222
Leu Ser Glu Ala Gln Phe Pro Pro Lys Trp
                740                 745
```

<210> 84
<211> 74
<212> PRT
<213> erythrovirus

<400> 84

```
Met Gln Met Pro Ser Thr Gln Ile Ser Lys Pro Pro Pro Leu Ser Gln
  1               5                  10                  15

Thr Pro Val Ser Ala Ala Val Val Val Lys Ala Leu Lys Asn Ser Val
             20                  25                  30

Lys Ala Ala Phe Ser Thr Ser Ser Leu Gln Ala Pro Gly Thr Val Lys
         35                  40                  45

Pro Arg Ala Leu Val Arg Pro Ser Pro Gly Pro Val Gln Glu Asn His
     50                  55                  60

Leu Ser Glu Ala Gln Phe Pro Pro Lys Trp
 65                  70
```

<210> 85
<211> 2343
<212> DNA

<213> erythrovirus

<400> 85

```
atg agt aaa acc act aac aaa tgg tgg gaa agc agt gac aaa ttt gcc      48
Met Ser Lys Thr Thr Asn Lys Trp Trp Glu Ser Ser Asp Lys Phe Ala
 75                  80                  85                  90

cag gac gtg tat aag cag ttt gtg caa ttt tat gaa aaa gct act gga      96
Gln Asp Val Tyr Lys Gln Phe Val Gln Phe Tyr Glu Lys Ala Thr Gly
                95                 100                 105

aca gac tta gag ctt att caa att tta aaa gac cat tac aac att tct     144
Thr Asp Leu Glu Leu Ile Gln Ile Leu Lys Asp His Tyr Asn Ile Ser
            110                 115                 120

tta gat aat cct tta gaa aac ccc tct tct tta ttt gac tta gtt gct     192
Leu Asp Asn Pro Leu Glu Asn Pro Ser Ser Leu Phe Asp Leu Val Ala
        125                 130                 135

cgc att aaa agt aat ctt aaa aac tct cca gac cta tat agt cat cat     240
Arg Ile Lys Ser Asn Leu Lys Asn Ser Pro Asp Leu Tyr Ser His His
    140                 145                 150

ttt cag agc cat gga cag tta tct gac cac ccc cat gcc tta tca tcc     288
Phe Gln Ser His Gly Gln Leu Ser Asp His Pro His Ala Leu Ser Ser
155                 160                 165                 170

agt aac agt agt gca gaa cct aga gga gaa aat gca gta tta tct agt     336
Ser Asn Ser Ser Ala Glu Pro Arg Gly Glu Asn Ala Val Leu Ser Ser
                175                 180                 185

gaa gac tta cac aag cct ggg caa gtt agc ata caa tta ccc ggt act     384
Glu Asp Leu His Lys Pro Gly Gln Val Ser Ile Gln Leu Pro Gly Thr
            190                 195                 200

aac tat gtt ggg cct ggc aat gag cta caa gct ggg cct ccg cag aat     432
Asn Tyr Val Gly Pro Gly Asn Glu Leu Gln Ala Gly Pro Pro Gln Asn
        205                 210                 215

gct gtg gac agt gct gca agg att cat gac ttt agg tat agc caa ttg     480
Ala Val Asp Ser Ala Ala Arg Ile His Asp Phe Arg Tyr Ser Gln Leu
    220                 225                 230

gct aag ttg gga ata aat cct tat aca cat tgg acg gta gca gat gaa     528
Ala Lys Leu Gly Ile Asn Pro Tyr Thr His Trp Thr Val Ala Asp Glu
235                 240                 245                 250

gaa ttg tta aaa aat ata aaa aat gaa aca ggg ttt caa gca caa gca     576
Glu Leu Leu Lys Asn Ile Lys Asn Glu Thr Gly Phe Gln Ala Gln Ala
                255                 260                 265 .

gta aaa gat tac ttt act tta aaa ggt gca gct gcc cct gtg gcc cat     624
Val Lys Asp Tyr Phe Thr Leu Lys Gly Ala Ala Ala Pro Val Ala His
            270                 275                 280

ttt caa gga agt tta ccg gaa gtg ccc gcg tac aac gcc tca gaa aaa     672
Phe Gln Gly Ser Leu Pro Glu Val Pro Ala Tyr Asn Ala Ser Glu Lys
        285                 290                 295
```

```
tac ccc agc atg act tca gtt aac tct gca gaa gcc agc act ggt gca     720
Tyr Pro Ser Met Thr Ser Val Asn Ser Ala Glu Ala Ser Thr Gly Ala
    300                 305                 310

ggc ggg gga ggt agc aac cct aca aaa agc atg tgg agt gaa ggg gct     768
Gly Gly Gly Gly Ser Asn Pro Thr Lys Ser Met Trp Ser Glu Gly Ala
315                 320                 325                 330

aca ttt act gct aat tct gta acg tgt aca ttc tct agg caa ttt tta     816
Thr Phe Thr Ala Asn Ser Val Thr Cys Thr Phe Ser Arg Gln Phe Leu
                335                 340                 345

att cca tat gat cca gag cat cat tat aaa gtg ttc tct cca gca gct     864
Ile Pro Tyr Asp Pro Glu His His Tyr Lys Val Phe Ser Pro Ala Ala
            350                 355                 360

agt agc tgc cac aat gct agt ggg aaa gag gca aaa gtg tgc act att     912
Ser Ser Cys His Asn Ala Ser Gly Lys Glu Ala Lys Val Cys Thr Ile
        365                 370                 375

agt ccc att atg ggg tac tct act ccg tgg aga tac tta gat ttt aat     960
Ser Pro Ile Met Gly Tyr Ser Thr Pro Trp Arg Tyr Leu Asp Phe Asn
    380                 385                 390

gct tta aat ttg ttt ttc tca cca tta gag ttt cag cac tta att gaa    1008
Ala Leu Asn Leu Phe Phe Ser Pro Leu Glu Phe Gln His Leu Ile Glu
395                 400                 405                 410

aat tat ggt agt ata gct cca gat gct tta act gta act att tca gaa    1056
Asn Tyr Gly Ser Ile Ala Pro Asp Ala Leu Thr Val Thr Ile Ser Glu
                415                 420                 425

att gct gta aaa gat gtc aca gac aaa aca gga gga ggt gtg caa gtt    1104
Ile Ala Val Lys Asp Val Thr Asp Lys Thr Gly Gly Gly Val Gln Val
            430                 435                 440

act gac agc acc aca gga cgt ttg tgt atg tta gtg gat cat gag tat    1152
Thr Asp Ser Thr Thr Gly Arg Leu Cys Met Leu Val Asp His Glu Tyr
        445                 450                 455

aaa tac cca tat gtg cta ggt cag gga caa gac aca cta gct cca gaa    1200
Lys Tyr Pro Tyr Val Leu Gly Gln Gly Gln Asp Thr Leu Ala Pro Glu
    460                 465                 470

ctg ccc att tgg gtt tac ttt ccc ccc cag tat gct tac tta aca gta    1248
Leu Pro Ile Trp Val Tyr Phe Pro Pro Gln Tyr Ala Tyr Leu Thr Val
475                 480                 485                 490

ggt gaa gta aac aca caa gga att tca gga gac agc aaa aaa ttg gct    1296
Gly Glu Val Asn Thr Gln Gly Ile Ser Gly Asp Ser Lys Lys Leu Ala
                495                 500                 505

agt gaa gaa tca gct ttt tat gtg tta gag cac agt tca ttt gaa ctt    1344
Ser Glu Glu Ser Ala Phe Tyr Val Leu Glu His Ser Ser Phe Glu Leu
            510                 515                 520

ttg ggt aca ggg gga tct gcc act atg tcc tac aaa ttt cca gct gtg    1392
Leu Gly Thr Gly Gly Ser Ala Thr Met Ser Tyr Lys Phe Pro Ala Val
        525                 530                 535
```

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ccc cca gaa aac cta gaa ggc tgc agc caa cat ttt tat gaa atg tac    1440
Pro Pro Glu Asn Leu Glu Gly Cys Ser Gln His Phe Tyr Glu Met Tyr
    540                 545                 550

aac cct ttg tac ggt tct cgt tta ggg gta cct gac aca tta gga ggg    1488
Asn Pro Leu Tyr Gly Ser Arg Leu Gly Val Pro Asp Thr Leu Gly Gly
555                 560                 565                 570

gac cct aaa ttt aga tca ttg aca cac gaa gac cac gca att cag cca    1536
Asp Pro Lys Phe Arg Ser Leu Thr His Glu Asp His Ala Ile Gln Pro
                575                 580                 585

caa aac ttt atg cct ggg cca cta ata aat tca gtg tct acc aaa gaa    1584
Gln Asn Phe Met Pro Gly Pro Leu Ile Asn Ser Val Ser Thr Lys Glu
            590                 595                 600

gga gac aat tct aat aca ggt gct gga aaa gcc ctt acg ggg ctt agt    1632
Gly Asp Asn Ser Asn Thr Gly Ala Gly Lys Ala Leu Thr Gly Leu Ser
        605                 610                 615

act ggc act agc caa aac acc aga att tcc cta cgc ccc ggg cca gta    1680
Thr Gly Thr Ser Gln Asn Thr Arg Ile Ser Leu Arg Pro Gly Pro Val
    620                 625                 630

tct cag cca tac cat cac tgg gac act gat aaa tat gtt aca gga ata    1728
Ser Gln Pro Tyr His His Trp Asp Thr Asp Lys Tyr Val Thr Gly Ile
635                 640                 645                 650

aat gcc att tca cat gga caa acc act tat gga aat gct gag gac aaa    1776
Asn Ala Ile Ser His Gly Gln Thr Thr Tyr Gly Asn Ala Glu Asp Lys
                655                 660                 665

gag tat cag caa ggg gta gga aga ttt cca aat gaa aaa gaa cag ctt    1824
Glu Tyr Gln Gln Gly Val Gly Arg Phe Pro Asn Glu Lys Glu Gln Leu
            670                 675                 680

aag cag tta caa ggt ctt aac atg cac aca tac ttc cct aat aaa gga    1872
Lys Gln Leu Gln Gly Leu Asn Met His Thr Tyr Phe Pro Asn Lys Gly
        685                 690                 695

acc caa caa tac aca gac caa att gaa cgc cct ctt atg gtg ggc tct    1920
Thr Gln Gln Tyr Thr Asp Gln Ile Glu Arg Pro Leu Met Val Gly Ser
    700                 705                 710

gtt tgg aac aga aga gct ctt cac tat gaa agt cag ctg tgg agt aaa    1968
Val Trp Asn Arg Arg Ala Leu His Tyr Glu Ser Gln Leu Trp Ser Lys
715                 720                 725                 730

atc cct aac tta gat gac agt ttt aaa act caa ttt gca gcc cta ggc    2016
Ile Pro Asn Leu Asp Asp Ser Phe Lys Thr Gln Phe Ala Ala Leu Gly
                735                 740                 745

ggg tgg ggt ttg cat caa cca ccc cct caa ata ttt tta aaa ata cta    2064
Gly Trp Gly Leu His Gln Pro Pro Pro Gln Ile Phe Leu Lys Ile Leu
            750                 755                 760
```

```
cca caa agt ggg cca att gga ggt att aaa tcc atg gga att act act    2112
Pro Gln Ser Gly Pro Ile Gly Gly Ile Lys Ser Met Gly Ile Thr Thr
        765                 770                 775

tta gtt caa tat gct gtg gga ata atg aca gtt acc atg acc ttt aaa    2160
Leu Val Gln Tyr Ala Val Gly Ile Met Thr Val Thr Met Thr Phe Lys
    780                 785                 790

ttg gga cct cga aag gct act gga agg tgg aat ccc cag cct ggc gtt    2208
Leu Gly Pro Arg Lys Ala Thr Gly Arg Trp Asn Pro Gln Pro Gly Val
795                 800                 805                 810

tat cct cct cat gca gct ggt cat tta cca tat gta ctg tat gac ccc    2256
Tyr Pro Pro His Ala Ala Gly His Leu Pro Tyr Val Leu Tyr Asp Pro
                815                 820                 825

aca gct aca gat gca aag caa cac cac aga cac gga tat gaa aag cct    2304
Thr Ala Thr Asp Ala Lys Gln His His Arg His Gly Tyr Glu Lys Pro
            830                 835                 840

gaa gaa ttg tgg act gcc aaa agc cgt gtg cac cca ttg                2343
Glu Glu Leu Trp Thr Ala Lys Ser Arg Val His Pro Leu
        845                 850                 855
```

<210> 86
<211> 781
<212> PRT
<213> erythrovirus

<400> 86

```
Met Ser Lys Thr Thr Asn Lys Trp Trp Glu Ser Ser Asp Lys Phe Ala
  1               5                  10                  15

Gln Asp Val Tyr Lys Gln Phe Val Gln Phe Tyr Glu Lys Ala Thr Gly
             20                  25                  30

Thr Asp Leu Glu Leu Ile Gln Ile Leu Lys Asp His Tyr Asn Ile Ser
         35                  40                  45

Leu Asp Asn Pro Leu Glu Asn Pro Ser Ser Leu Phe Asp Leu Val Ala
     50                  55                  60

Arg Ile Lys Ser Asn Leu Lys Asn Ser Pro Asp Leu Tyr Ser His His
 65                  70                  75                  80

Phe Gln Ser His Gly Gln Leu Ser Asp His Pro His Ala Leu Ser Ser
                 85                  90                  95

Ser Asn Ser Ser Ala Glu Pro Arg Gly Glu Asn Ala Val Leu Ser Ser
            100                 105                 110

Glu Asp Leu His Lys Pro Gly Gln Val Ser Ile Gln Leu Pro Gly Thr
        115                 120                 125

Asn Tyr Val Gly Pro Gly Asn Glu Leu Gln Ala Gly Pro Pro Gln Asn
    130                 135                 140

Ala Val Asp Ser Ala Ala Arg Ile His Asp Phe Arg Tyr Ser Gln Leu
145                 150                 155                 160
```

```
Ala Lys Leu Gly Ile Asn Pro Tyr Thr His Trp Thr Val Ala Asp Glu
                165                 170                 175

Glu Leu Leu Lys Asn Ile Lys Asn Glu Thr Gly Phe Gln Ala Gln Ala
            180                 185                 190

Val Lys Asp Tyr Phe Thr Leu Lys Gly Ala Ala Ala Pro Val Ala His
        195                 200                 205

Phe Gln Gly Ser Leu Pro Glu Val Pro Ala Tyr Asn Ala Ser Glu Lys
    210                 215                 220

Tyr Pro Ser Met Thr Ser Val Asn Ser Ala Glu Ala Ser Thr Gly Ala
225                 230                 235                 240

Gly Gly Gly Gly Ser Asn Pro Thr Lys Ser Met Trp Ser Glu Gly Ala
                245                 250                 255

Thr Phe Thr Ala Asn Ser Val Thr Cys Thr Phe Ser Arg Gln Phe Leu
            260                 265                 270

Ile Pro Tyr Asp Pro Glu His His Tyr Lys Val Phe Ser Pro Ala Ala
        275                 280                 285

Ser Ser Cys His Asn Ala Ser Gly Lys Glu Ala Lys Val Cys Thr Ile
    290                 295                 300

Ser Pro Ile Met Gly Tyr Ser Thr Pro Trp Arg Tyr Leu Asp Phe Asn
305                 310                 315                 320

Ala Leu Asn Leu Phe Phe Ser Pro Leu Glu Phe Gln His Leu Ile Glu
                325                 330                 335

Asn Tyr Gly Ser Ile Ala Pro Asp Ala Leu Thr Val Thr Ile Ser Glu
            340                 345                 350

Ile Ala Val Lys Asp Val Thr Asp Lys Thr Gly Gly Gly Val Gln Val
        355                 360                 365

Thr Asp Ser Thr Thr Gly Arg Leu Cys Met Leu Val Asp His Glu Tyr
    370                 375                 380

Lys Tyr Pro Tyr Val Leu Gly Gln Gly Gln Asp Thr Leu Ala Pro Glu
385                 390                 395                 400

Leu Pro Ile Trp Val Tyr Phe Pro Pro Gln Tyr Ala Tyr Leu Thr Val
                405                 410                 415

Gly Glu Val Asn Thr Gln Gly Ile Ser Gly Asp Ser Lys Lys Leu Ala
            420                 425                 430

Ser Glu Glu Ser Ala Phe Tyr Val Leu Glu His Ser Ser Phe Glu Leu
        435                 440                 445

Leu Gly Thr Gly Gly Ser Ala Thr Met Ser Tyr Lys Phe Pro Ala Val
    450                 455                 460
```

```
Pro Pro Glu Asn Leu Glu Gly Cys Ser Gln His Phe Tyr Glu Met Tyr
465                 470                 475                 480

Asn Pro Leu Tyr Gly Ser Arg Leu Gly Val Pro Asp Thr Leu Gly Gly
                485                 490                 495

Asp Pro Lys Phe Arg Ser Leu Thr His Glu Asp His Ala Ile Gln Pro
            500                 505                 510

Gln Asn Phe Met Pro Gly Pro Leu Ile Asn Ser Val Ser Thr Lys Glu
        515                 520                 525

Gly Asp Asn Ser Asn Thr Gly Ala Gly Lys Ala Leu Thr Gly Leu Ser
    530                 535                 540

Thr Gly Thr Ser Gln Asn Thr Arg Ile Ser Leu Arg Pro Gly Pro Val
545                 550                 555                 560

Ser Gln Pro Tyr His His Trp Asp Thr Asp Lys Tyr Val Thr Gly Ile
                565                 570                 575

Asn Ala Ile Ser His Gly Gln Thr Thr Tyr Gly Asn Ala Glu Asp Lys
            580                 585                 590

Glu Tyr Gln Gln Gly Val Gly Arg Phe Pro Asn Glu Lys Glu Gln Leu
        595                 600                 605

Lys Gln Leu Gln Gly Leu Asn Met His Thr Tyr Phe Pro Asn Lys Gly
    610                 615                 620

Thr Gln Gln Tyr Thr Asp Gln Ile Glu Arg Pro Leu Met Val Gly Ser
625                 630                 635                 640

Val Trp Asn Arg Arg Ala Leu His Tyr Glu Ser Gln Leu Trp Ser Lys
                645                 650                 655

Ile Pro Asn Leu Asp Asp Ser Phe Lys Thr Gln Phe Ala Ala Leu Gly
            660                 665                 670

Gly Trp Gly Leu His Gln Pro Pro Pro Gln Ile Phe Leu Lys Ile Leu
        675                 680                 685

Pro Gln Ser Gly Pro Ile Gly Gly Ile Lys Ser Met Gly Ile Thr Thr
    690                 695                 700

Leu Val Gln Tyr Ala Val Gly Ile Met Thr Val Thr Met Thr Phe Lys
705                 710                 715                 720

Leu Gly Pro Arg Lys Ala Thr Gly Arg Trp Asn Pro Gln Pro Gly Val
                725                 730                 735

Tyr Pro Pro His Ala Ala Gly His Leu Pro Tyr Val Leu Tyr Asp Pro
            740                 745                 750

Thr Ala Thr Asp Ala Lys Gln His His Arg His Gly Tyr Glu Lys Pro
        755                 760                 765

Glu Glu Leu Trp Thr Ala Lys Ser Arg Val His Pro Leu
    770                 775                 780
```

<210> 87
<211> 681
<212> DNA
<213> erythrovirus

<400> 87

```
atg agt aaa acc act aac aaa tgg tgg gaa agc agt gac aaa ttt gcc      48
Met Ser Lys Thr Thr Asn Lys Trp Trp Glu Ser Ser Asp Lys Phe Ala
            785                 790                 795

cag gac gtg tat aag cag ttt gtg caa ttt tat gaa aaa gct act gga      96
Gln Asp Val Tyr Lys Gln Phe Val Gln Phe Tyr Glu Lys Ala Thr Gly
        800                 805                 810

aca gac tta gag ctt att caa att tta aaa gac cat tac aac att tct     144
Thr Asp Leu Glu Leu Ile Gln Ile Leu Lys Asp His Tyr Asn Ile Ser
    815                 820                 825

tta gat aat cct tta gaa aac ccc tct tct tta ttt gac tta gtt gct     192
Leu Asp Asn Pro Leu Glu Asn Pro Ser Ser Leu Phe Asp Leu Val Ala
830                 835                 840                 845

cgc att aaa agt aat ctt aaa aac tct cca gac cta tat agt cat cat     240
Arg Ile Lys Ser Asn Leu Lys Asn Ser Pro Asp Leu Tyr Ser His His
                850                 855                 860

ttt cag agc cat gga cag tta tct gac cac ccc cat gcc tta tca tcc     288
Phe Gln Ser His Gly Gln Leu Ser Asp His Pro His Ala Leu Ser Ser
            865                 870                 875

agt aac agt agt gca gaa cct aga gga gaa aat gca gta tta tct agt     336
Ser Asn Ser Ser Ala Glu Pro Arg Gly Glu Asn Ala Val Leu Ser Ser
        880                 885                 890

gaa gac tta cac aag cct ggg caa gtt agc ata caa tta ccc ggt act     384
Glu Asp Leu His Lys Pro Gly Gln Val Ser Ile Gln Leu Pro Gly Thr
    895                 900                 905

aac tat gtt ggg cct ggc aat gag cta caa gct ggg cct ccg cag aat     432
Asn Tyr Val Gly Pro Gly Asn Glu Leu Gln Ala Gly Pro Pro Gln Asn
910                 915                 920                 925

gct gtg gac agt gct gca agg att cat gac ttt agg tat agc caa ttg     480
Ala Val Asp Ser Ala Ala Arg Ile His Asp Phe Arg Tyr Ser Gln Leu
                930                 935                 940

gct aag ttg gga ata aat cct tat aca cat tgg acg gta gca gat gaa     528
Ala Lys Leu Gly Ile Asn Pro Tyr Thr His Trp Thr Val Ala Asp Glu
            945                 950                 955

gaa ttg tta aaa aat ata aaa aat gaa aca ggg ttt caa gca caa gca     576
Glu Leu Leu Lys Asn Ile Lys Asn Glu Thr Gly Phe Gln Ala Gln Ala
        960                 965                 970

gta aaa gat tac ttt act tta aaa ggt gca gct gcc cct gtg gcc cat     624
Val Lys Asp Tyr Phe Thr Leu Lys Gly Ala Ala Ala Pro Val Ala His
    975                 980                 985
```

```
ttt caa gga agt tta ccg gaa gtg ccc gcg tac aac gcc tca gaa aaa     672
Phe Gln Gly Ser Leu Pro Glu Val Pro Ala Tyr Asn Ala Ser Glu Lys
990                 995                 1000                1005

tac ccc agc                                                        681
Tyr Pro Ser
```

<210> 88
<211> 227
<212> PRT
<213> erythrovirus

<400> 88

```
Met Ser Lys Thr Thr Asn Lys Trp Trp Glu Ser Ser Asp Lys Phe Ala
  1               5                  10                  15

Gln Asp Val Tyr Lys Gln Phe Val Gln Phe Tyr Glu Lys Ala Thr Gly
             20                  25                  30

Thr Asp Leu Glu Leu Ile Gln Ile Leu Lys Asp His Tyr Asn Ile Ser
         35                  40                  45

Leu Asp Asn Pro Leu Glu Asn Pro Ser Ser Leu Phe Asp Leu Val Ala
     50                  55                  60

Arg Ile Lys Ser Asn Leu Lys Asn Ser Pro Asp Leu Tyr Ser His His
 65                  70                  75                  80

Phe Gln Ser His Gly Gln Leu Ser Asp His Pro His Ala Leu Ser Ser
                 85                  90                  95

Ser Asn Ser Ser Ala Glu Pro Arg Gly Glu Asn Ala Val Leu Ser Ser
            100                 105                 110

Glu Asp Leu His Lys Pro Gly Gln Val Ser Ile Gln Leu Pro Gly Thr
        115                 120                 125

Asn Tyr Val Gly Pro Gly Asn Glu Leu Gln Ala Gly Pro Pro Gln Asn
    130                 135                 140

Ala Val Asp Ser Ala Ala Arg Ile His Asp Phe Arg Tyr Ser Gln Leu
145                 150                 155                 160

Ala Lys Leu Gly Ile Asn Pro Tyr Thr His Trp Thr Val Ala Asp Glu
                165                 170                 175

Glu Leu Leu Lys Asn Ile Lys Asn Glu Thr Gly Phe Gln Ala Gln Ala
            180                 185                 190

Val Lys Asp Tyr Phe Thr Leu Lys Gly Ala Ala Ala Pro Val Ala His
        195                 200                 205

Phe Gln Gly Ser Leu Pro Glu Val Pro Ala Tyr Asn Ala Ser Glu Lys
    210                 215                 220

Tyr Pro Ser
225
```

<210> 89
<211> 306
<212> DNA
<213> erythrovirus

<400> 89

```
ttg ctc gca tta aaa gta atc tta aaa act ctc cag acc tat ata gtc      48
Leu Leu Ala Leu Lys Val Ile Leu Lys Thr Leu Gln Thr Tyr Ile Val
        230                 235                 240

atc att ttc aga gcc atg gac agt tat ctg acc acc ccc atg cct tat      96
Ile Ile Phe Arg Ala Met Asp Ser Tyr Leu Thr Thr Pro Met Pro Tyr
    245                 250                 255

cat cca gta aca gta gtg cag aac cta gag gag aaa atg cag tat tat     144
His Pro Val Thr Val Val Gln Asn Leu Glu Glu Lys Met Gln Tyr Tyr
260                 265                 270                 275

cta gtg aag act tac aca agc ctg ggc aag tta gca tac aat tac ccg     192
Leu Val Lys Thr Tyr Thr Ser Leu Gly Lys Leu Ala Tyr Asn Tyr Pro
                280                 285                 290

gta cta act atg ttg ggc ctg gca atg agc tac aag ctg ggc ctc cgc     240
Val Leu Thr Met Leu Gly Leu Ala Met Ser Tyr Lys Leu Gly Leu Arg
            295                 300                 305

aga atg ctg tgg aca gtg ctg caa gga ttc atg act tta ggt ata gcc     288
Arg Met Leu Trp Thr Val Leu Gln Gly Phe Met Thr Leu Gly Ile Ala
        310                 315                 320

aat tgg cta agt tgg gaa                                            306
Asn Trp Leu Ser Trp Glu
    325
```

<210> 90
<211> 102
<212> PRT
<213> erythrovirus

<400> 90

```
Leu Leu Ala Leu Lys Val Ile Leu Lys Thr Leu Gln Thr Tyr Ile Val
  1               5                  10                  15

Ile Ile Phe Arg Ala Met Asp Ser Tyr Leu Thr Thr Pro Met Pro Tyr
             20                  25                  30

His Pro Val Thr Val Val Gln Asn Leu Glu Glu Lys Met Gln Tyr Tyr
         35                  40                  45

Leu Val Lys Thr Tyr Thr Ser Leu Gly Lys Leu Ala Tyr Asn Tyr Pro
     50                  55                  60

Val Leu Thr Met Leu Gly Leu Ala Met Ser Tyr Lys Leu Gly Leu Arg
 65                  70                  75                  80

Arg Met Leu Trp Thr Val Leu Gln Gly Phe Met Thr Leu Gly Ile Ala
                 85                  90                  95
```

Asn Trp Leu Ser Trp Glu
100

<210> 91
<211> 1662
<212> DNA
<213> erythrovirus

<400> 91

```
atg act tca gtt aac tct gca gaa gcc agc act ggt gca ggc ggg gga      48
Met Thr Ser Val Asn Ser Ala Glu Ala Ser Thr Gly Ala Gly Gly Gly
        105                 110                 115

ggt agc aac cct aca aaa agc atg tgg agt gaa ggg gct aca ttt act      96
Gly Ser Asn Pro Thr Lys Ser Met Trp Ser Glu Gly Ala Thr Phe Thr
    120                 125                 130

gct aat tct gta acg tgt aca ttc tct agg caa ttt tta att cca tat     144
Ala Asn Ser Val Thr Cys Thr Phe Ser Arg Gln Phe Leu Ile Pro Tyr
135                 140                 145                 150

gat cca gag cat cat tat aaa gtg ttc tct cca gca gct agt agc tgc     192
Asp Pro Glu His His Tyr Lys Val Phe Ser Pro Ala Ala Ser Ser Cys
                155                 160                 165

cac aat gct agt ggg aaa gag gca aaa gtg tgc act att agt ccc att     240
His Asn Ala Ser Gly Lys Glu Ala Lys Val Cys Thr Ile Ser Pro Ile
            170                 175                 180

atg ggg tac tct act ccg tgg aga tac tta gat ttt aat gct tta aat     288
Met Gly Tyr Ser Thr Pro Trp Arg Tyr Leu Asp Phe Asn Ala Leu Asn
        185                 190                 195

ttg ttt ttc tca cca tta gag ttt cag cac tta att gaa aat tat ggt     336
Leu Phe Phe Ser Pro Leu Glu Phe Gln His Leu Ile Glu Asn Tyr Gly
    200                 205                 210

agt ata gct cca gat gct tta act gta act att tca gaa att gct gta     384
Ser Ile Ala Pro Asp Ala Leu Thr Val Thr Ile Ser Glu Ile Ala Val
215                 220                 225                 230

aaa gat gtc aca gac aaa aca gga gga ggt gtg caa gtt act gac agc     432
Lys Asp Val Thr Asp Lys Thr Gly Gly Gly Val Gln Val Thr Asp Ser
                235                 240                 245

acc aca gga cgt ttg tgt atg tta gtg gat cat gag tat aaa tac cca     480
Thr Thr Gly Arg Leu Cys Met Leu Val Asp His Glu Tyr Lys Tyr Pro
            250                 255                 260

tat gtg cta ggt cag gga caa gac aca cta gct cca gaa ctg ccc att     528
Tyr Val Leu Gly Gln Gly Gln Asp Thr Leu Ala Pro Glu Leu Pro Ile
        265                 270                 275

tgg gtt tac ttt ccc ccc cag tat gct tac tta aca gta ggt gaa gta     576
Trp Val Tyr Phe Pro Pro Gln Tyr Ala Tyr Leu Thr Val Gly Glu Val
    280                 285                 290
```

```
aac aca caa gga att tca gga gac agc aaa aaa ttg gct agt gaa gaa      624
Asn Thr Gln Gly Ile Ser Gly Asp Ser Lys Lys Leu Ala Ser Glu Glu
295                 300                 305                 310

tca gct ttt tat gtg tta gag cac agt tca ttt gaa ctt ttg ggt aca      672
Ser Ala Phe Tyr Val Leu Glu His Ser Ser Phe Glu Leu Leu Gly Thr
                315                 320                 325

ggg gga tct gcc act atg tcc tac aaa ttt cca gct gtg ccc cca gaa      720
Gly Gly Ser Ala Thr Met Ser Tyr Lys Phe Pro Ala Val Pro Pro Glu
            330                 335                 340

aac cta gaa ggc tgc agc caa cat ttt tat gaa atg tac aac cct ttg      768
Asn Leu Glu Gly Cys Ser Gln His Phe Tyr Glu Met Tyr Asn Pro Leu
        345                 350                 355

tac ggt tct cgt tta ggg gta cct gac aca tta gga ggg gac cct aaa      816
Tyr Gly Ser Arg Leu Gly Val Pro Asp Thr Leu Gly Gly Asp Pro Lys
    360                 365                 370

ttt aga tca ttg aca cac gaa gac cac gca att cag cca caa aac ttt      864
Phe Arg Ser Leu Thr His Glu Asp His Ala Ile Gln Pro Gln Asn Phe
375                 380                 385                 390

atg cct ggg cca cta ata aat tca gtg tct acc aaa gaa gga gac aat      912
Met Pro Gly Pro Leu Ile Asn Ser Val Ser Thr Lys Glu Gly Asp Asn
                395                 400                 405

tct aat aca ggt gct gga aaa gcc ctt acg ggg ctt agt act ggc act      960
Ser Asn Thr Gly Ala Gly Lys Ala Leu Thr Gly Leu Ser Thr Gly Thr
            410                 415                 420

agc caa aac acc aga att tcc cta cgc ccc ggg cca gta tct cag cca     1008
Ser Gln Asn Thr Arg Ile Ser Leu Arg Pro Gly Pro Val Ser Gln Pro
        425                 430                 435

tac cat cac tgg gac act gat aaa tat gtt aca gga ata aat gcc att     1056
Tyr His His Trp Asp Thr Asp Lys Tyr Val Thr Gly Ile Asn Ala Ile
    440                 445                 450

tca cat gga caa acc act tat gga aat gct gag gac aaa gag tat cag     1104
Ser His Gly Gln Thr Thr Tyr Gly Asn Ala Glu Asp Lys Glu Tyr Gln
455                 460                 465                 470

caa ggg gta gga aga ttt cca aat gaa aaa gaa cag ctt aag cag tta     1152
Gln Gly Val Gly Arg Phe Pro Asn Glu Lys Glu Gln Leu Lys Gln Leu
                475                 480                 485

caa ggt ctt aac atg cac aca tac ttc cct aat aaa gga acc caa caa     1200
Gln Gly Leu Asn Met His Thr Tyr Phe Pro Asn Lys Gly Thr Gln Gln
            490                 495                 500

tac aca gac caa att gaa cgc cct ctt atg gtg ggc tct gtt tgg aac     1248
Tyr Thr Asp Gln Ile Glu Arg Pro Leu Met Val Gly Ser Val Trp Asn
        505                 510                 515

aga aga gct ctt cac tat gaa agt cag ctg tgg agt aaa atc cct aac     1296
Arg Arg Ala Leu His Tyr Glu Ser Gln Leu Trp Ser Lys Ile Pro Asn
    520                 525                 530
```

```
tta gat gac agt ttt aaa act caa ttt gca gcc cta ggc ggg tgg ggt    1344
Leu Asp Asp Ser Phe Lys Thr Gln Phe Ala Ala Leu Gly Gly Trp Gly
535                 540                 545                 550

ttg cat caa cca ccc cct caa ata ttt tta aaa ata cta cca caa agt    1392
Leu His Gln Pro Pro Pro Gln Ile Phe Leu Lys Ile Leu Pro Gln Ser
                555                 560                 565

ggg cca att gga ggt att aaa tcc atg gga att act act tta gtt caa    1440
Gly Pro Ile Gly Gly Ile Lys Ser Met Gly Ile Thr Thr Leu Val Gln
            570                 575                 580

tat gct gtg gga ata atg aca gtt acc atg acc ttt aaa ttg gga cct    1488
Tyr Ala Val Gly Ile Met Thr Val Thr Met Thr Phe Lys Leu Gly Pro
        585                 590                 595

cga aag gct act gga agg tgg aat ccc cag cct ggc gtt tat cct cct    1536
Arg Lys Ala Thr Gly Arg Trp Asn Pro Gln Pro Gly Val Tyr Pro Pro
    600                 605                 610

cat gca gct ggt cat tta cca tat gta ctg tat gac ccc aca gct aca    1584
His Ala Ala Gly His Leu Pro Tyr Val Leu Tyr Asp Pro Thr Ala Thr
615                 620                 625                 630

gat gca aag caa cac cac aga cac gga tat gaa aag cct gaa gaa ttg    1632
Asp Ala Lys Gln His His Arg His Gly Tyr Glu Lys Pro Glu Glu Leu
                635                 640                 645

tgg act gcc aaa agc cgt gtg cac cca ttg                           1662
Trp Thr Ala Lys Ser Arg Val His Pro Leu
            650                 655
```

<210> 92
<211> 554
<212> PRT
<213> erythrovirus

<400> 92

```
Met Thr Ser Val Asn Ser Ala Glu Ala Ser Thr Gly Ala Gly Gly Gly
  1               5                  10                  15

Gly Ser Asn Pro Thr Lys Ser Met Trp Ser Glu Gly Ala Thr Phe Thr
             20                  25                  30

Ala Asn Ser Val Thr Cys Thr Phe Ser Arg Gln Phe Leu Ile Pro Tyr
         35                  40                  45

Asp Pro Glu His His Tyr Lys Val Phe Ser Pro Ala Ala Ser Ser Cys
     50                  55                  60

His Asn Ala Ser Gly Lys Glu Ala Lys Val Cys Thr Ile Ser Pro Ile
 65                  70                  75                  80

Met Gly Tyr Ser Thr Pro Trp Arg Tyr Leu Asp Phe Asn Ala Leu Asn
                 85                  90                  95

Leu Phe Phe Ser Pro Leu Glu Phe Gln His Leu Ile Glu Asn Tyr Gly
            100                 105                 110
```

```
Ser Ile Ala Pro Asp Ala Leu Thr Val Thr Ile Ser Glu Ile Ala Val
        115                 120                 125

Lys Asp Val Thr Asp Lys Thr Gly Gly Gly Val Gln Val Thr Asp Ser
    130                 135                 140

Thr Thr Gly Arg Leu Cys Met Leu Val Asp His Glu Tyr Lys Tyr Pro
145                 150                 155                 160

Tyr Val Leu Gly Gln Gly Gln Asp Thr Leu Ala Pro Glu Leu Pro Ile
                165                 170                 175

Trp Val Tyr Phe Pro Pro Gln Tyr Ala Tyr Leu Thr Val Gly Glu Val
            180                 185                 190

Asn Thr Gln Gly Ile Ser Gly Asp Ser Lys Lys Leu Ala Ser Glu Glu
        195                 200                 205

Ser Ala Phe Tyr Val Leu Glu His Ser Ser Phe Glu Leu Leu Gly Thr
    210                 215                 220

Gly Gly Ser Ala Thr Met Ser Tyr Lys Phe Pro Ala Val Pro Pro Glu
225                 230                 235                 240

Asn Leu Glu Gly Cys Ser Gln His Phe Tyr Glu Met Tyr Asn Pro Leu
                245                 250                 255

Tyr Gly Ser Arg Leu Gly Val Pro Asp Thr Leu Gly Gly Asp Pro Lys
            260                 265                 270

Phe Arg Ser Leu Thr His Glu Asp His Ala Ile Gln Pro Gln Asn Phe
        275                 280                 285

Met Pro Gly Pro Leu Ile Asn Ser Val Ser Thr Lys Glu Gly Asp Asn
    290                 295                 300

Ser Asn Thr Gly Ala Gly Lys Ala Leu Thr Gly Leu Ser Thr Gly Thr
305                 310                 315                 320

Ser Gln Asn Thr Arg Ile Ser Leu Arg Pro Gly Pro Val Ser Gln Pro
                325                 330                 335

Tyr His His Trp Asp Thr Asp Lys Tyr Val Thr Gly Ile Asn Ala Ile
            340                 345                 350

Ser His Gly Gln Thr Thr Tyr Gly Asn Ala Glu Asp Lys Glu Tyr Gln
        355                 360                 365

Gln Gly Val Gly Arg Phe Pro Asn Glu Lys Glu Gln Leu Lys Gln Leu
    370                 375                 380

Gln Gly Leu Asn Met His Thr Tyr Phe Pro Asn Lys Gly Thr Gln Gln
385                 390                 395                 400

Tyr Thr Asp Gln Ile Glu Arg Pro Leu Met Val Gly Ser Val Trp Asn
                405                 410                 415
```

```
Arg Arg Ala Leu His Tyr Glu Ser Gln Leu Trp Ser Lys Ile Pro Asn
            420                 425                 430

Leu Asp Asp Ser Phe Lys Thr Gln Phe Ala Ala Leu Gly Gly Trp Gly
        435                 440                 445

Leu His Gln Pro Pro Pro Gln Ile Phe Leu Lys Ile Leu Pro Gln Ser
    450                 455                 460

Gly Pro Ile Gly Gly Ile Lys Ser Met Gly Ile Thr Thr Leu Val Gln
465                 470                 475                 480

Tyr Ala Val Gly Ile Met Thr Val Thr Met Thr Phe Lys Leu Gly Pro
                485                 490                 495

Arg Lys Ala Thr Gly Arg Trp Asn Pro Gln Pro Gly Val Tyr Pro Pro
            500                 505                 510

His Ala Ala Gly His Leu Pro Tyr Val Leu Tyr Asp Pro Thr Ala Thr
        515                 520                 525

Asp Ala Lys Gln His His Arg His Gly Tyr Glu Lys Pro Glu Glu Leu
    530                 535                 540

Trp Thr Ala Lys Ser Arg Val His Pro Leu
545                 550

<210> 93
<211> 396
<212> DNA
<213> erythrovirus

<400> 93
cct tta aat tgg gac ctc gaa agg cta ctg gaa ggt gga atc ccc agc      48
Pro Leu Asn Trp Asp Leu Glu Arg Leu Leu Glu Gly Gly Ile Pro Ser
555                 560                 565                 570

ctg gcg ttt atc ctc ctc atg cag ctg gtc att tac cat atg tac tgt      96
Leu Ala Phe Ile Leu Leu Met Gln Leu Val Ile Tyr His Met Tyr Cys
                575                 580                 585

atg acc cca cag cta cag atg caa agc aac acc aca gac acg gat atg     144
Met Thr Pro Gln Leu Gln Met Gln Ser Asn Thr Thr Asp Thr Asp Met
            590                 595                 600

aaa agc ctg aag aat tgt gga ctg cca aaa gcc gtg tgc acc cat tgt     192
Lys Ser Leu Lys Asn Cys Gly Leu Pro Lys Ala Val Cys Thr His Cys
        605                 610                 615

aaa cat tcc cca ccg tgt cct cag cca gga acc gtc acc cac cgc cca     240
Lys His Ser Pro Pro Cys Pro Gln Pro Gly Thr Val Thr His Arg Pro
    620                 625                 630

cct gtg ccg ccc aga tta tat gtg ccc cct cca ata ccc cgt agg caa     288
Pro Val Pro Pro Arg Leu Tyr Val Pro Pro Pro Ile Pro Arg Arg Gln
635                 640                 645                 650
```

```
cca tct ata aaa gat aca gac gct gta gaa tat aaa tta tta act aga      336
Pro Ser Ile Lys Asp Thr Asp Ala Val Glu Tyr Lys Leu Leu Thr Arg
                655                 660                 665

tat gaa caa cat gta att aga atg cta aga tta tgt aat atg tac aca      384
Tyr Glu Gln His Val Ile Arg Met Leu Arg Leu Cys Asn Met Tyr Thr
            670                 675                 680

agt ttg gaa aaa                                                     396
Ser Leu Glu Lys
        685
```

<210> 94
<211> 132
<212> PRT
<213> erythrovirus

<400> 94

```
Pro Leu Asn Trp Asp Leu Glu Arg Leu Leu Glu Gly Gly Ile Pro Ser
  1               5                  10                  15

Leu Ala Phe Ile Leu Leu Met Gln Leu Val Ile Tyr His Met Tyr Cys
             20                  25                  30

Met Thr Pro Gln Leu Gln Met Gln Ser Asn Thr Thr Asp Thr Asp Met
         35                  40                  45

Lys Ser Leu Lys Asn Cys Gly Leu Pro Lys Ala Val Cys Thr His Cys
     50                  55                  60

Lys His Ser Pro Pro Cys Pro Gln Pro Gly Thr Val Thr His Arg Pro
 65                  70                  75                  80

Pro Val Pro Pro Arg Leu Tyr Val Pro Pro Pro Ile Pro Arg Arg Gln
                 85                  90                  95

Pro Ser Ile Lys Asp Thr Asp Ala Val Glu Tyr Lys Leu Leu Thr Arg
            100                 105                 110

Tyr Glu Gln His Val Ile Arg Met Leu Arg Leu Cys Asn Met Tyr Thr
        115                 120                 125

Ser Leu Glu Lys
    130
```

<210> 95
<211> 40
<212> PRT
<213> erythrovirus

<400> 95

```
     Met Ser Lys Thr Thr Asn Lys Trp Trp Glu Ser Ser Asp Lys Phe Ala
     1               5                  10                  15

     Gln Asp Val Tyr Lys Gln Phe Val Gln Phe Tyr Glu Lys Ala Thr Gly
                 20                  25                  30

     Thr Asp Leu Glu Leu Ile Gln Ile
             35                  40
```

<210> 96
<211> 21
<212> PRT
<213> erythrovirus

<400> 96
Ser Leu Phe Asp Leu Val Ala Arg Ile Lys Ser Asn Leu Lys Asn Ser
1 5 10 15

Pro Asp Leu Tyr Ser
20

<210> 97
<211> 24
<212> PRT
<213> erythrovirus

<400> 97
Leu Ser Asp His Pro His Ala Leu Ser Ser Ser Asn Ser Ser Ala Glu
1 5 10 15

Pro Arg Gly Glu Asn Ala Val Leu
20

<210> 98
<211> 21
<212> PRT
<213> erythrovirus

<400> 98
Glu Asp Leu His Lys Pro Gly Gln Val Ser Ile Gln Leu Pro Gly Thr
1 5 10 15

Asn Tyr Val Gly Pro
20

<210> 99
<211> 22
<212> PRT
<213> erythrovirus

<400> 99
Gly Asn Glu Leu Gln Ala Gly Pro Pro Gln Asn Ala Val Asp Ser Ala
1 5 10 15

Ala Arg Ile His Asp Phe
20

<210> 100
<211> 21
<212> PRT
<213> erythrovirus

<400> 100
Ile Lys Asn Glu Thr Gly Phe Gln Ala Gln Ala Val Lys Asp Tyr Phe
1 5 10 15

Thr Leu Lys Gly Ala
20

<210> 101
<211> 32
<212> PRT
<213> erythrovirus

<400> 101
Ser Thr Gly Ala Gly Gly Gly Gly Ser Asn Pro Thr Lys Ser Met Trp
1 5 10 15

Ser Glu Gly Ala Thr Phe Thr Ala Asn Ser Val Thr Cys Thr Phe Ser
20 25 30

<210> 102
<211> 21
<212> PRT
<213> erythrovirus

<400> 102
Pro Pro Gln Tyr Ala Tyr Leu Thr Val Gly Glu Val Asn Thr Gln Gly
1 5 10 15

Ile Ser Gly Asp Ser
20

<210> 103
<211> 37
<212> PRT
<213> erythrovirus

<400> 103
Ala Phe Tyr Val Leu Glu His Ser Ser Phe Glu Leu Leu Gly Thr Gly
1 5 10 15

Gly Ser Ala Thr Met Ser Tyr Lys Phe Pro Ala Val Pro Pro Glu Asn
20 25 30

Leu Glu Gly Cys Ser
35

<210> 104
<211> 28
<212> PRT
<213> erythrovirus

<400> 104
Gln Asn Phe Met Pro Gly Pro Leu Ile Asn Ser Val Ser Thr Lys Glu
1 5 10 15

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